

10/581566

AP20 Rec'd PCT/PTO 02 JUN 2006
Attorney Docket No.: 61810-5002-US02

UNITED STATES OF AMERICA

PATENT APPLICATION

PRACTICAL, COST-EFFECTIVE SYNTHESIS OF UBIQUINONES

Inventor(s):

BRUCE H. LIPSHUTZ, a citizen of the United States of America
residing at 452 Albany Court,
Goleta, California 93117

VOLKER BERL, a citizen of the Federal Republic of Germany,
residing at 2, rond point de l'Esplanade
67000 Strasbourg, France

KARIN SCHEIN, a citizen of the Federal Republic of Germany,
residing at Krongasse 17
67065 Ludwigshafen, Germany

FRANK WETTERICH, a citizen of the Federal Republic of Germany,
residing at Hans-Willmann-Str. 11
67157 Wachenheim, Germany

Assignee:

Zymes, LLC
500 Route 17 South
Hasbrouck Heights, NJ 07604

Entity: Small

Jeffrey S. Mann
Reg. No. 42,837

MORGAN LEWIS AND
BOCKIUS LLP

Correspondence
Address:

Two Palo Alto Square
3000 El Camino Real, Suite 700
Palo Alto, California 94306
Tel 415 442-1000
Fax 650-843-4001

AS FILED WITH THE PCT ON JUNE 2, 2006

10/581566

AP20 Rec'd PCT/PTO 02 JUN 2006

Attorney Docket No.: 61810-5002-US02

PRACTICAL, COST-EFFECTIVE SYNTHESIS OF UBIQUINONES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application is a U.S. national phase application of PCT Application No. PCT/US2004/040565, filed December 3, 2004, and claims priority to United States Provisional Patent Application Number 60/527,513, filed on December 5, 2003, the disclosures of which are incorporated herein by reference in their entirety for all purposes.

BACKGROUND OF THE INVENTION

[0002] The ubiquinones, also commonly called coenzyme Q_n (n = 1-12), constitute essential cellular components of many life forms. In humans, CoQ₁₀ is the predominant member of this class of polyprenoidal natural products and is well-known to function primarily as a redox carrier in the respiratory chain (Lenaz, COENZYME Q. BIOCHEMISTRY, BIOENERGETICS, AND CLINICAL APPLICATIONS OF UBIQUINONE, Wiley-Interscience: New York (1985); Trumpower, FUNCTION OF UBIQUINONES IN ENERGY CONSERVING SYSTEMS, Academic Press, New York (1982); Thomson, R. H., NATURALLY OCCURRING QUINONES, 3rd ed., Academic Press, New York (1987); Bliznakov *et al.*, THE MIRACLE NUTRIENT COENZYME Q₁₀, Bantom Books, New York (1987)).

[0003] Coenzyme Q plays an essential role in the orchestration of electron-transfer processes necessary for respiration. Almost all vertebrates rely on one or more forms of this series of compounds that are found in the mitochondria of every cell (*i.e.*, they are ubiquitous, hence the alternative name "ubiquinones"). Although usually occurring with up to 12 prenoidal units attached to a *p*-quinone headgroup, CoQ₁₀ is the compound used by humans as a redox carrier. Oftentimes unappreciated is the fact that when less than normal levels are present, the body must construct its CoQ₁₀ from lower forms obtained through the diet, and that at some point in everyone's life span the efficiency of that machinery begins to drop. (Blizakov *et al.*, *supra*) The consequences of this *in vivo* deterioration can be substantial; levels of CoQ₁₀ have been correlated with increased sensitivity to infection (*i.e.*, a weakening of the immune system), strength of heart muscle, and metabolic rates tied to

energy levels and vigor. In the United States, however, it is considered a dietary supplement, sold typically in health food stores or through mail order houses at reasonable prices. It is indeed fortunate that quantities of CoQ₁₀ are available via well-established fermentation and extraction processes (*e.g.*, Sasikala *et al.*, *Adv. Appl. Microbiol.*, **41**:173 (1995); U.S. Patent No. 4,447,362; 3,313,831; and 3,313,826) an apparently more cost-efficient route relative to total synthesis. However, for producing lower forms of CoQ, such processes are either far less efficient or are unknown. Thus, the costs of these materials for research purposes are astonishingly high, *e.g.*, CoQ₆ is ~\$22,000/g, and CoQ₉ is over \$40,000/g. (Sigma-Aldrich Catalog, Sigma-Aldrich: St. Louis, pp. 306-307 (1998)).

[0004] Several approaches to synthesizing the ubiquinones have been developed over the past 3-4 decades, attesting to the importance of these compounds. Recent contributions have invoked such varied approaches as Lewis acid-induced prenoidal stannane additions to quinones, (Naruta, *J. Org. Chem.*, **45**:4097 (1980)) reiterative Pd(0)-catalyzed couplings of doubly activated prenoidal chains with allylic carbonates bearing the required aromatic nucleus in protected form (Eren *et al.*, *J. Am. Chem. Soc.*, **110**:4356 (1988) and references therein), and a Diels—Alder, retro Diels—Alder route to arrive at the quinone oxidation state directly (Van Lient *et al.*, *Rec. Trav. Chim. Pays-Bas* **113**:153 (1994); and Rüttiman *et al.*, *Helv. Chim. Acta*, **73**:790 (1990)). Nonetheless, all are lengthy, linear rather than convergent, and/or inefficient. Moreover, problems in controlling double bond stereochemistry using, *e.g.*, a copper(I)-catalyzed allylic Grignard-allylic halide coupling can lead to complicated mixtures of geometrical isomers that are difficult to separate given the hydrocarbon nature of the side chains (Yanagisawa, *et al.*, *Synthesis*, 1130 (1991)).

[0005] Another method of producing ubiquinones has been developed by Negishi (Negishi, *Org. Lett.* **4**(2): 261-264 (2002)). In this publication, Negishi describes a traditional carboalumination of unactivated alkynes. This method possesses some characteristics that limit its applicability for industrial uses. For example, the reactions in Negishi are conducted in chlorinated solvents, which can constitute a significant waste removal expense. In addition, the use of large amounts of ≥ 25 mole % of a zirconocene species in the carboalumination reaction creates vinylic alanes in the presence of zirconium salts that perform with less than optimal efficiency in subsequent coupling reactions with key chloromethylated quinones as substrates. Thus, the zirconocene salts necessitate their costly separation from the vinyl alane to be used in the coupling, significantly impacting the economic costs of the process.

[0006] For the reasons set forth above, a convergent method for the synthesis of the ubiquinones and their analogues which originates with a simple benzenoid precursor and proceeds with retention of the double bond stereochemistry would represent a significant advance in the synthesis of ubiquinones and their analogues. The present invention provides such a method and ubiquinone precursors of use in the method.

SUMMARY OF THE INVENTION

[0007] The present invention provides an efficient and inexpensive method for preparing ubiquinones and structural analogues of these essential molecules. Also provided are new compounds that are structurally simple and provide a convenient, efficient and inexpensive entry into the method of the invention.

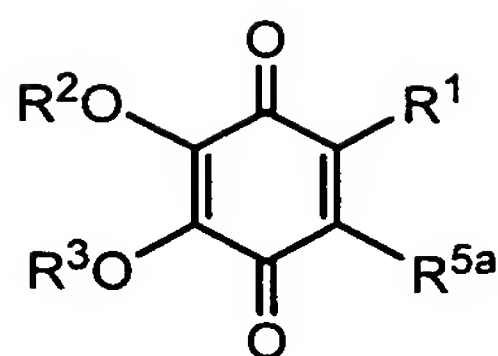
[0008] Thus, in a first aspect, the present invention provides a compound according to Formula (I):



In Formula (I), R¹, R² and R³ are independently selected substituted or unsubstituted C₁-C₆ alkyl groups, *e.g.*, methyl groups. R⁴ represents H, substituted or unsubstituted alkyl, *e.g.*, methyl, or a protecting group. R⁵ is selected from branched, unsaturated alkyl, -CH(O) (formyl), and -CH₂Y, in which Y can be OR⁷, SR⁷, NR⁷R⁸, or a leaving group. R⁷ and R⁸ are independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl. R⁶ is H, -OCH(O), or another group that is readily converted to a quinone carbonyl moiety.

[0009] In an exemplary embodiment, when R⁵ is -CH(O) or Y is a leaving group, *e.g.*, halo, then R⁶ is OCH(O).

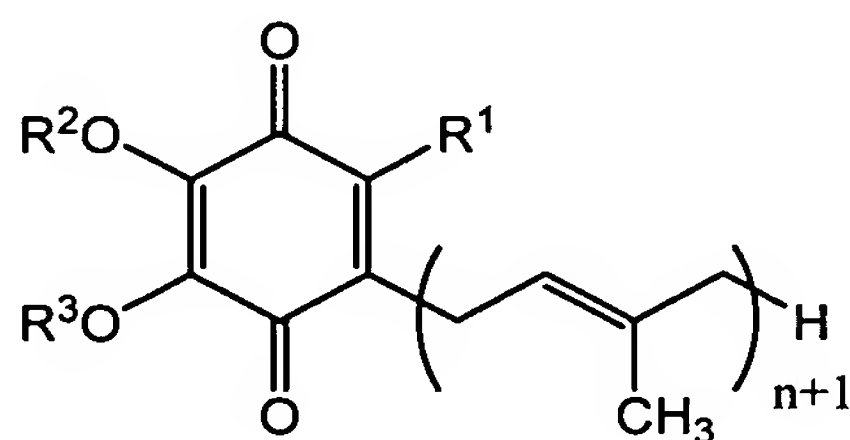
[0010] In a second aspect, the invention provides compounds according to Formula (II):



(II)

in which R^1 , R^2 and R^3 are as described for Formula (I) and R^{5a} is $-\text{CH}(\text{O})$ or CH_2OR^7 .

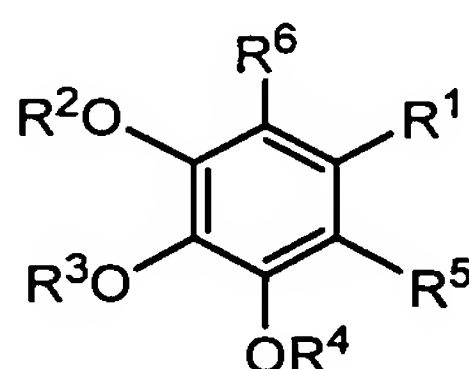
[0011] In a third aspect, the present invention provides methods for preparing a ubiquinone according to Formula (III):



(III).

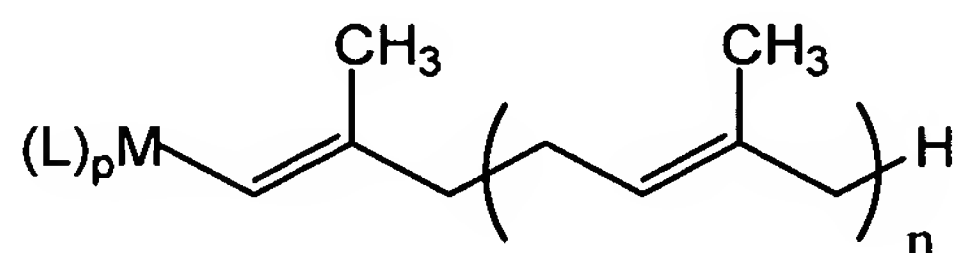
In Formula (III), each of R^1 , R^2 and R^3 are substituents as described for Formula (I), and the subscript n represents an integer from 0 to 19.

[0012] Thus, an exemplary method of the invention includes contacting a compound according to Formula (I):



(I)

with a compound according to Formula (IV):

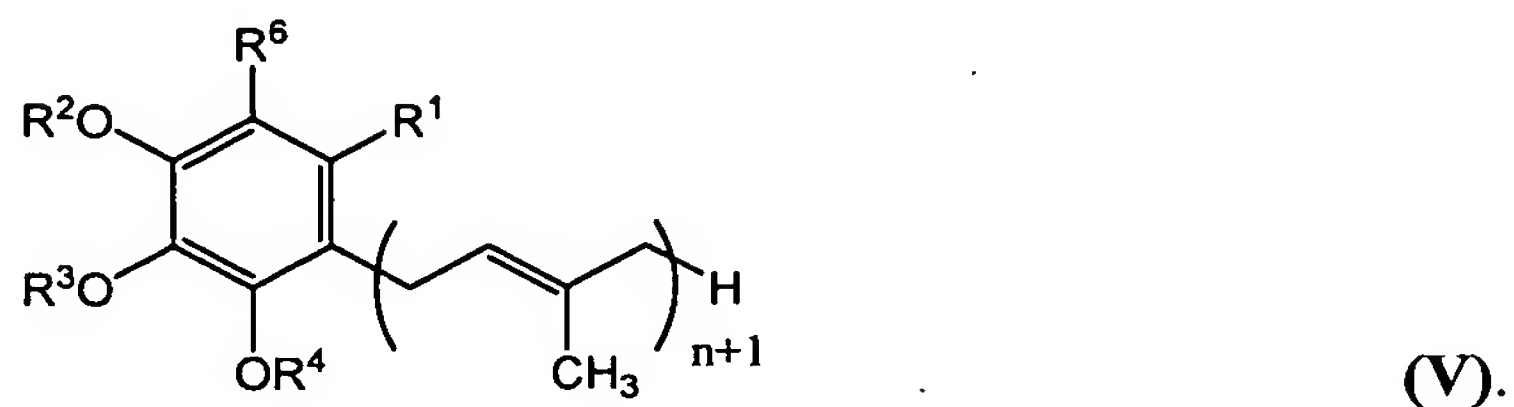


(IV)

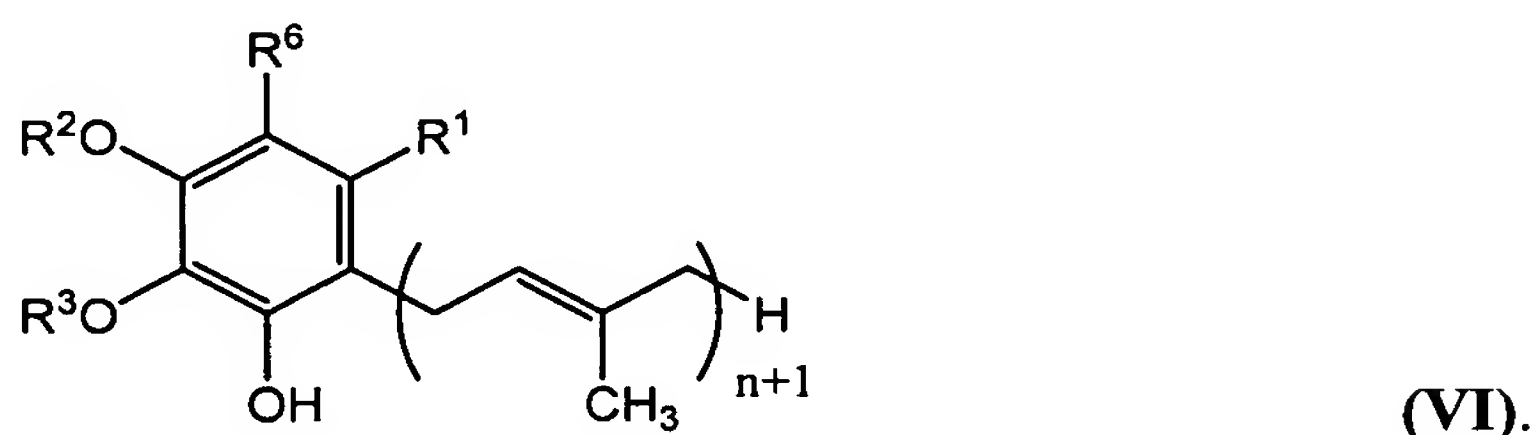
in which each L is an independently selected organic ligand or substituent, *e.g.*, substituted or unsubstituted alkyl; M is aluminum; p is 1 or 2; and n is an integer from 0 to 19. Each of the organic ligands (substituents) L , can be the same or different. R^1 - R^6 are as discussed above.

[0013] The mixture of compounds according to Formulae (I) and (IV) are contacted with a coupling catalyst, *e.g.*, $\text{Ni}(0)$ that is effective at catalyzing coupling between a benzylic carbon atom, such as that in Formula (I), and an organometallic species according to

Formula (IV). The coupling of the compounds of Formulae (I) and (IV) forms a compound according to Formula (V):



R^4 is preferably removed from the compound according to Formula (V) to produce a compound according to Formula (VI), in which n represents an integer from 0 to 19:



Contacting the compound according to Formula (VI) with an oxidant yields a compound according to Formula (III).

[0014] In another aspect, the invention provides a method for preparing a ubiquinone by direct coupling of an alkene to a substituted-methylene quinone (*e.g.*, an ether, sulfonate, etc.). Thus, a compound according to Formula (II):



is contacted with a compound according to Formula (IV) in the presence of a coupling catalyst. An exemplary coupling catalyst is a nickel catalyst.

[0015] In a still further aspect, the invention provides a reaction pathway that includes the direct coupling of a compound according to Formula (IV) with a halomethyl quinone having the formula:



in which X is a leaving group, *e.g.*, halogen, and R¹-R³ are as defined above.

[0016] In still another aspect the invention provides a method of carboaluminating an alkyne substrate, forming a species with an alkyl moiety bound to aluminium, said method comprising contacting said alkyne substrate with (L)_{p+1}M and x molar equivalents of water or R²⁰OH, or, when each L is methyl, with x molar equivalents of water, R²⁰OH or methylaluminoxane relative to said alkyne substrate, wherein

$$0 < x < 1;$$

each L is independently selected from substituted or unsubstituted alkyl, alkoxy, aryl or aryloxy with 1 to 10 carbon atoms;

M is aluminium;

p is 1 or 2 and,

R²⁰ is branched or unbranched alkyl with 1 to 15 carbon atoms, optionally substituted with 1 to 5 hydroxy substituents,

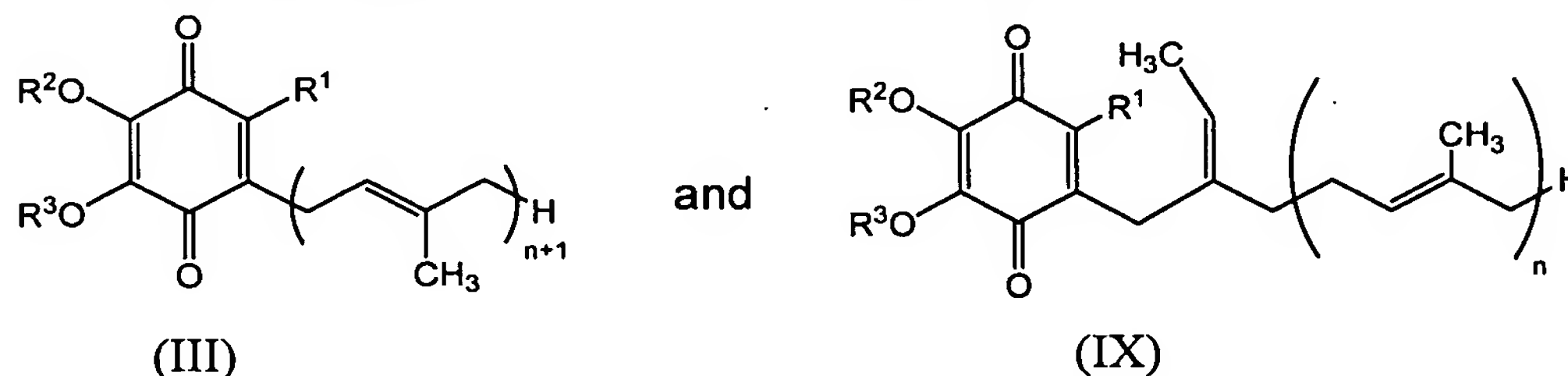
thus carboaluminating said alkyne substrate .

[0017] The present invention also provides a method of preparing ubiquinones and their analogues that does not require the use of halogenated reaction solvents.

[0018] Also provided is a method of preparing a compound according to Formula (VII) as shown in FIG. 1. The invention also provides novel methods of purification that allow for ready access to a chloromethylated quinone (VII, X = Cl), prepared in two steps from trimethoxytoluene, as outlined in FIG. 4, that is suitable for use directly in the coupling step to produce CoQ_{n+1}.

[0019] Other methods of the invention utilize a metal catalyst, *e.g.*, a zirconocene or titanocene, in a catalytic process to carboaluminate, *e.g.*, carboaluminate a substrate. An exemplary compound formed by this method is set forth in Formula (IV).

[0020] In still a further aspect, the invention provides a mixture comprising:



wherein R¹, R² and R³ are members independently selected from substituted or unsubstituted

C₁-C₆ alkyl groups, and n is an integer from 0 to 19.

[0021] Other objects and advantages of the invention will be apparent to those of skill in the art from the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] FIG. 1 sets forth representative intermediates and transformations of use in the process of the invention.

[0023] FIG. 2 sets forth a method of producing an ubiquinone.

[0024] FIG. 3 sets forth another method of producing an ubiquinone.

[0025] FIG. 4 sets forth a method of converting an aromatic moiety into a substituted methylene quinone and a haloquinone.

DETAILED DESCRIPTION OF THE INVENTION AND THE PREFERRED EMBODIMENTS

Definitions

[0026] The term “alkyl,” by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multi-valent radicals, having the number of carbon atoms designated (*i.e.* C₁-C₁₀ means one to ten carbons). Examples of saturated hydrocarbon radicals include groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)ethyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers. The term “alkyl,” unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below as “heteroalkyl,” “cycloalkyl” and “alkylene.” The term “alkylene” by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by -CH₂CH₂CH₂CH₂-. Typically, an alkyl group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present

invention. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0027] The terms “alkoxy,” “alkylamino” and “alkylthio” refer to those groups having an alkyl group attached to the remainder of the molecule through an oxygen, nitrogen or sulfur atom, respectively. Similarly, the term “dialkylamino” is used in a conventional sense to refer to $-NR'R''$ wherein the R groups can be the same or different alkyl groups.

[0028] The term “acyl” or “alkanoyl” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and an acyl radical on at least one terminus of the alkane radical.

[0029] The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. Examples include $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$, and $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$ and $-\text{CH}_2-\text{O}-\text{Si}(\text{CH}_3)_3$. Also included in the term “heteroalkyl” are those radicals described in more detail below as “heteroalkylene” and “heterocycloalkyl.” The term “heteroalkylene” by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini. Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied.

[0030] The terms “cycloalkyl” and “heterocycloalkyl”, by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of “alkyl” and “heteroalkyl”, respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the

position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

[0031] The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “fluoroalkyl,” are meant to include monofluoroalkyl and polyfluoroalkyl.

[0032] The term “aryl,” employed alone or in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) means, unless otherwise stated, an aromatic substituent which can be a single ring or multiple rings (up to three rings), which are fused together or linked covalently. “Heteroaryl” are those aryl groups having at least one heteroatom ring member. Typically, the rings each contain from zero to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. The “heteroaryl” groups can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalyl, 5-quinoxalyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl ring systems are selected from the group of acceptable substituents described below. The term “arylalkyl” is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) or a heteroalkyl group (*e.g.*, phenoxyethyl, 2-pyridyloxyethyl, 3-(1-naphthyloxy)propyl, and the like).

[0033] Each of the above terms (*e.g.*, “alkyl,” “heteroalkyl” and “aryl”) are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0034] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be a variety of groups selected from, for example: -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -CN and -NO₂ in a number ranging from zero to (2N+ 1), where N is the total number of carbon atoms in such radical. R', R'' and R''' each independently refer to hydrogen, unsubstituted (C₁-C₈)alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-(C₁-C₄)alkyl groups. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R'' is meant to include 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups such as haloalkyl (*e.g.*, -CF₃ and -CH₂CF₃) and acyl (*e.g.*, -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

[0035] Similarly, substituents for the aryl groups are varied and are selected from: -halogen, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R'', -C(O)R', -OC(O)NR'R'', -NR''C(O)R', -NR''C(O)₂R', -NR'-C(O)NR''R''', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -N₃, -CH(Ph)₂, perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'' and R''' are independently selected from hydrogen, (C₁-C₈)alkyl and heteroalkyl, unsubstituted aryl, (unsubstituted aryl)-(C₁-C₄)alkyl, (unsubstituted aryl)oxy-(C₁-C₄)alkyl and perfluoro(C₁-C₄)alkyl.

[0036] Two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH₂)_q-U-, wherein T and U are independently -NH-, -O-, -CH₂- or a single bond, and the subscript q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CH₂-, -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of

the aryl ring may optionally be replaced with a substituent of the formula $-(CH_2)_s-X-(CH_2)_t-$, where s and t are independently integers of from 0 to 3, and X is $-O-$, $-NR'-$, $-S-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituent R' in $-NR'-$ and $-S(O)_2NR'-$ is selected from hydrogen or unsubstituted (C_1-C_6) alkyl.

[0037] As used herein, the term “heteroatom” is meant to include, for example, oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0038] Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all encompassed within the scope of the present invention.

[0039] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

[0040] As used herein, the term “leaving group” refers to a portion of a substrate that is cleaved from the substrate in a reaction. The leaving group is an atom (or a group of atoms) that is displaced as stable species taking with it the bonding electrons. Typically the leaving group is an anion (*e.g.*, Cl^-) or a neutral molecule (*e.g.*, H_2O). Exemplary leaving groups include a halogen, $OC(O)R^9$, $OP(O)R^9R^{10}$, $OS(O)R^9$, and OSO_2R^9 . R^9 and R^{10} are members independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl. Useful leaving groups include, but are not limited to, other halides, sulfonic esters, oxonium ions, alkyl perchlorates, sulfonates, *e.g.*, arylsulfonates, ammonioalkanesulfonate esters, and alkylfluorosulfonates, phosphates, carboxylic acid esters, carbonates, ethers, and fluorinated compounds (*e.g.*, triflates, nonaflates, tresylates), S , R^9 , $(R^9)_3P^+$, $(R^9)_2S^+$, $P(O)N(R^9)_2(R^9)_2$, $P(O)XR^9X'R^9$ in which each R^9 is independently selected from the members provided in this paragraph and X and X' are S or O. The choice of these and other leaving groups appropriate for a particular set of reaction conditions is within the abilities of those of skill in the art (*see*, for example, March J, ADVANCED ORGANIC CHEMISTRY, 2nd Edition, John Wiley and Sons, 1992; Sandler SR, Karo W,

ORGANIC FUNCTIONAL GROUP PREPARATIONS, 2nd Edition, Academic Press, Inc., 1983; and Wade LG, COMPENDIUM OF ORGANIC SYNTHETIC METHODS, John Wiley and Sons, 1980).

[0041] "Protecting group," as used herein refers to a portion of a substrate that is substantially stable under a particular reaction condition, but which is cleaved from the substrate under a different reaction condition. A protecting group can also be selected such that it participates in the direct oxidation of the aromatic ring component of the compounds of the invention. For examples of useful protecting groups, *see*, for example, Greene *et al.*, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, 3rd ed., John Wiley & Sons, New York, 1999.

[0042] "Adsorbent", as used herein refers to a material with the property to hold molecules of fluids without causing a chemical or physical change. Examples are Silica gel, Alumina, Charcoal, Ion exchange resins and others, characterized by high surface/volume ratio.

Introduction

[0043] The present invention provides an efficient and cost-effective route to the ubiquinones and their analogues. The present method is quite general and can be used to afford CoQ_{n+1} and analogues as well as systems found in vitamins K₁ and K₂ and their analogues. The invention also provides compounds that are useful in the method of the invention.

[0044] As set forth herein, the invention also provides useful improvements in methods of purifying substituted-methylene quinones from halo-quinones, and methods of improved efficiency for carboaluminating an alkyne substrate.

The Compounds

[0045] In a first aspect, the present invention provides a compound according to Formula (I):



[0046] In Formula (I), R¹, R² and R³ are independently selected substituted or unsubstituted C₁-C₆ alkyl groups, preferably methyl groups. R⁴ represents H, substituted or unsubstituted alkyl, preferably methyl, a metal ion or a protecting group. R⁵ can be selected

from branched, unsaturated alkyl, $-\text{CH}(\text{O})$, and $-\text{CH}_2\text{Y}$, in which Y is OR^7 , SR^7 , NR^7R^8 , or a leaving group. In an exemplary embodiment, Y is OR^{7a} , in which R^{7a} , together with the oxygen to which it is bound, forms a leaving group.

[0047] R^7 and R^8 can be independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl. R^6 is H, OH or $-\text{OCH}(\text{O})$, or another group that is readily converted to a quinone ketone moiety or a phenyl H atom.

[0048] Exemplary substituents R^{7a} include $-\text{SOR}^9$, $-\text{SO}_2\text{R}^9$, $-\text{C}(\text{O})\text{R}^9$, $-\text{C}(\text{O})\text{OR}^9$, $-\text{P}(\text{O})\text{OR}^9\text{OR}^{10}$, $-\text{P}(\text{O})\text{N}(\text{R}^9)_2(\text{R}^{10})_2$, and $-\text{P}(\text{O})\text{R}^9\text{R}^{10}$. R^9 and R^{10} can be members independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl.

[0049] In an exemplary embodiment, when R^5 is $-\text{CH}(\text{O})$ or Y is a leaving group, *e.g.*, halo, then R^6 is $-\text{OCH}(\text{O})$. In another exemplary embodiment, R^5 has a structure according to Formula (VIII):



in which the symbol n can be selected from the integers from 0 to 19. In an exemplary embodiment, the symbol n can be selected from the integers from 0 to 13. In another exemplary embodiment, the symbol n can be selected from the integers from 4 to 10.

[0050] In a second aspect, the invention provides compounds according to Formula (II):

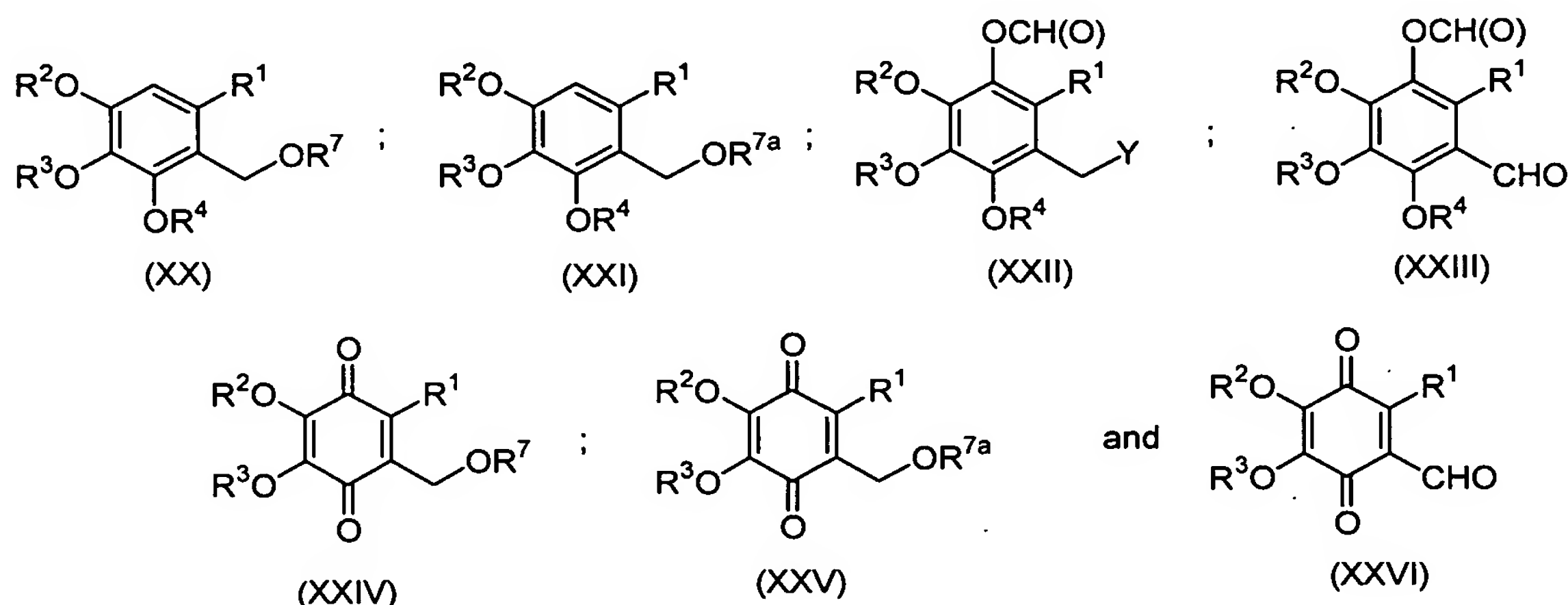


in which R^1 , R^2 and R^3 , and R^5 are as described for Formula (I). In another exemplary embodiment R^5 has a structure according to Formula (VIII):



in which the symbol n can be selected from the integers from 0 to 19. In an exemplary embodiment, the symbol n can be selected from the integers from 0 to 13. In another exemplary embodiment, the symbol n can be selected from the integers from 4 to 10.

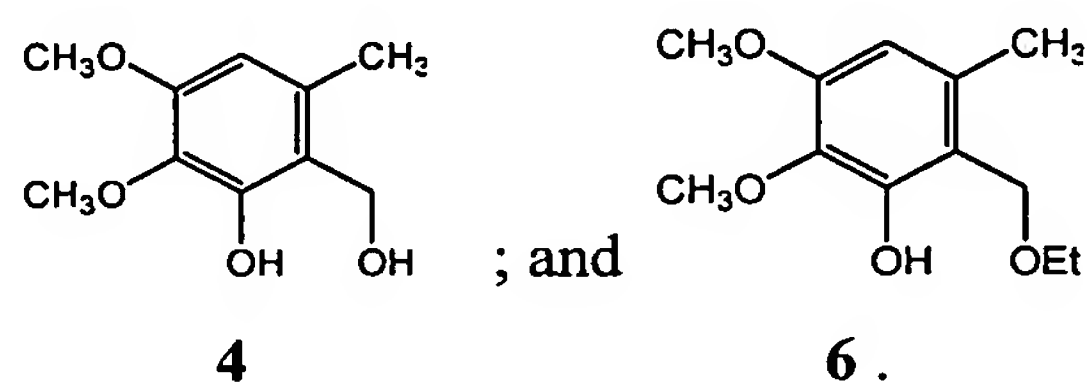
[0051] Exemplary compounds of the invention according to Formulae I and II include:



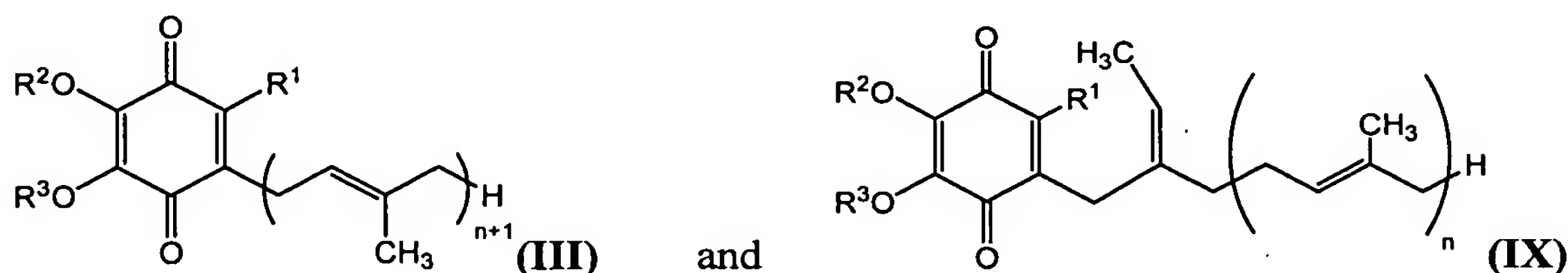
in which the identity of the substituents is as discussed hereinabove.

[0052] In still further exemplary compounds according to the invention, R^1 , R^2 , and R^3 can be methyl; and R^4 is methyl or H. In another exemplary embodiment, R^{7a} can be SOR^9 , SO_2R^9 , $C(O)R^9$, $C(O)OR^9$, $P(O)OR^9OR^{10}$, $P(O)N(R^9)_2(R^{10})_2$, and $P(O)R^9R^{10}$. R^9 and R^{10} can be independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl.

[0053] Further exemplary compounds of the invention include:



[0054] The invention also provides a mixture comprising the regioisomers according to Formulae (III) and (IX):



in which the symbols R^1 , R^2 and R^3 independently represent substituted or unsubstituted C_1 - C_6 alkyl groups; and the symbol n is an integer from 0 to 19. In a preferred embodiment R^1 , R^2 and R^3 in Formulae (III) and (IX) is methyl. Further preference is given to mixtures of compounds of Formulae (III) and (IX) in which the molar ratio of the compound of Formula (III) to the compound of Formula (IX) is at least 8 : 1.

Synthesis of the Compounds and Methods of the Invention

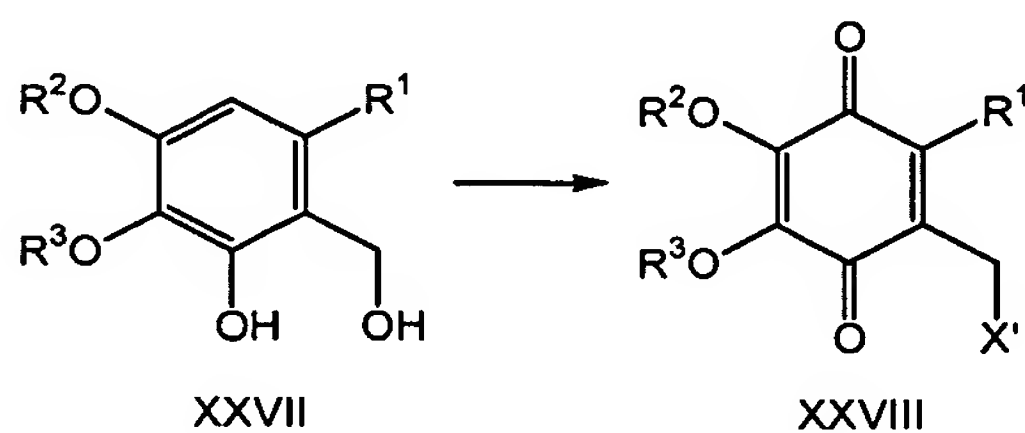
[0055] Techniques useful in synthesizing the compounds of the invention are both readily apparent and accessible to those of skill in the relevant art. The discussion below is offered to illustrate certain of the diverse methods available for use in assembling the compounds of the invention, it is not intended to define the scope of reactions or reaction sequences that are useful in preparing the compounds of the present invention.

Synthesis of the Starting Materials

Synthesis of the Substituted Methylene Moiety

[0056] The substituted methylene moieties of the invention are prepared by art-recognized methods or modifications thereof. For example, the synthesis of quinones functionalized with a halomethyl group can be accomplished using methods such as that described by Lipshutz (Lipshutz *et al.*, *J. Am. Chem. Soc.* **121**: 11664-11673 (1999)), the disclosure of which is incorporated herein by reference. In addition, the synthesis of substituted methylene aromatic moieties, such as phenols, can be accomplished using methods described by U.S. Patent No. 6,545,184 to Lipshutz *et al.*, the disclosure of which is also herein incorporated by reference.

[0057] In one aspect, the invention provides a method of preparing a substituted methylene moiety present in quinone (XXVIII) by performing the following transformation:



in which R¹, R² and R³ can each be independently selected from substituted or unsubstituted C₁-C₆ alkyl groups. X' is OH or a leaving group. In an exemplary embodiment, R¹, R² and R³ are methyl. In another exemplary embodiment, the method further comprises the synthesis of the substituted methylene moiety. Representative transformations for preparing this and other selected compounds of the invention are displayed in **FIG 1**. Commercially available **1** is formylated, yielding aldehyde **2**. The aldehyde is demethylated, affording phenol **3**, the aldehyde group of which is reduced to benzylic alcohol **4**.

[0058] A wide array of art-recognized reducing agents can be used to effect the transformation of the aldehyde **3** to the alcohol of **4**. *See*, for example, Trost *et al.*, COMPREHENSIVE ORGANIC SYNTHESIS: REDUCTION, Pergamon Press, 1992. In an exemplary embodiment, the reducing agent is a reagent that is a source of hydrogen which is a member selected from the group consisting of metal hydrides, and catalytic hydrogenation. In another exemplary embodiment, the reduction is an electrochemical reduction.

[0059] In another exemplary embodiment, contacting **4** with an oxidant converts it readily into the corresponding quinone **5**. The oxidative conversion of **4** to **5** is optionally performed under pressure that is greater than ambient pressure. Methods for conducting reactions under pressure are recognized in the art (*see, e.g.*, Matsumoto and Acheson, ORGANIC SYNTHESIS AT HIGH PRESSURE, J. Wiley & Sons, NY, 1991).

[0060] The hydroxyl moiety of **5** is contacted with a halogenating agent, such as thionyl chloride, affording halide **8**, which can be directly coupled to a vinyl alane according to the procedure of Negishi *et al.*, *Org. Lett.* **4**: 261 (2002). Alternatively, the hydroxyl moiety of **5** is alkylated, giving quinone ether **7**, or it is directly acylated, phosphorylated, sulfinated or sulfonated.

[0061] Rather than being oxidized to the corresponding quinone, **4** can be readily converted to a benzylic derivative with a leaving group, *e.g.*, an oxygen-containing moiety, at the benzylic carbon. In an exemplary embodiment, the moiety is benzylic ether **6**, which is prepared by contacting **4** with an alkylating agent. The benzylic ether is oxidized to quinone **7**. The leaving group is replaced by coupling a reagent according to Formula (IV) and the quinone in the presence of a catalyst.

[0062] The synthetic schemes set forth herein are intended to be exemplary of the synthesis compounds of the invention. Those of skill in the art will recognize that many other synthetic strategies leading to compounds within the scope of the present invention are

available. For example, by a slight modification of the starting material above, a compound having ethoxy, rather than methoxy groups is produced. Moreover, leaving and protecting groups discussed herein can be replaced with other useful groups having a similar function.

[0063] The reaction pathways set forth in **FIG. 1** and **FIG. 2** can be altered by using a leaving group other than a chloro at the methylene of **8**. Examples of useful leaving groups are provided herein.

[0064] Moreover, the methyl group used to protect the phenol oxygen atom can be replaced with a number of other art-recognized protecting groups. Useful phenol protecting groups include, but are not limited to, ethers formed between the phenol oxygen atom and substituted or unsubstituted alkyl groups (*e.g.*, sulfonic acid esters, methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, methylthiomethyl, phenylthiomethyl, 2,2-dichloro-1,1-difluoroethyl, tetrahydropyranyl, phenacyl, *p*-bromophenacyl, cyclopropylmethyl, allyl, isopropyl, cyclohexyl, *t*-butyl, benzyl, 2,6-dimethylbenzyl, 4-methoxybenzyl, *o*-nitrobenzyl, 2,6-dichlorobenzyl, 4-(dimethylaminocarbonyl)benzyl, 9-anthrylmethyl, 4-picolyl, heptafluoro-*p*-tolyl, tetrafluoro-4-pyridyl); silyl ethers (*e.g.*, trimethylsilyl, *t*-butyldimethylsilyl); esters (*e.g.*, acetate, levulinate, pivaloate, benzoate, 9-fluorene-9-carboxylate); carbonates (*e.g.*, methyl, 2,2,2-trichloroethyl, vinyl, benzyl); phosphinates (*e.g.*, dimethylphosphinyl, dimethylthiophosphinyl); sulfonates (*e.g.*, methanesulfonate, toluenesulfonate, 2-formylbenzenesulfonate), and the like (*see, e.g.*, Greene *et al.*, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, 3rd ed., John Wiley & Sons, New York, 1999).

[0065] In another exemplary embodiment, the compound of the invention includes a OCH(O) moiety as the R⁶ substituent of Formula (I). As shown in **FIG. 3**, the OCH(O) moiety is a protecting group that remains intact during the conversion of the formyl group of **10** to the chloromethyl group of **9**, and its alkylation to produce **32**. The OCH(O) group is removed by hydrolytic cleavage and the resulting hydroxyl derivative **33** is readily oxidized to the corresponding ubiquinone.

[0066] In another aspect, the invention provides a simple, inexpensive and effective purification strategy for a halomethyl quinone, prepared according to the route set forth in Fig. 4.

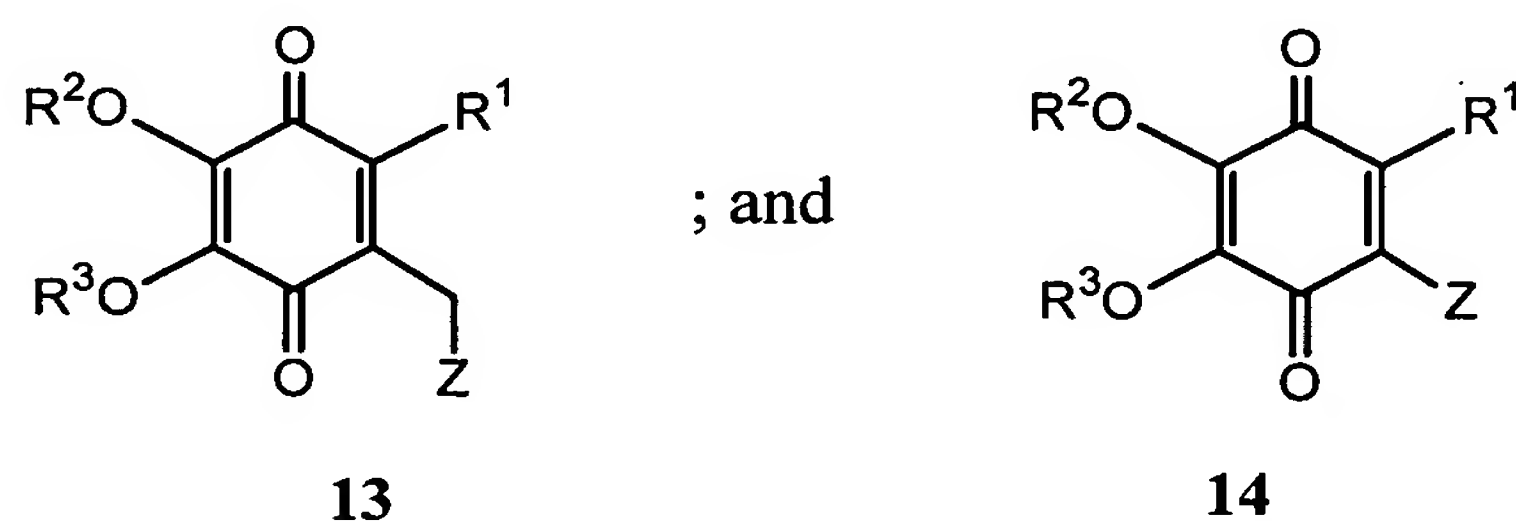
[0067] In the route outlined in **FIG. 4**, quinone **12** is prepared by oxidation of the trialkoxy (*e.g.*, trimethoxy) starting material. The quinone is converted to the corresponding

halomethyl derivative **13** by the action of formaldehyde in the presence of a selected halohydric acid. Although this route offers cost and time savings attributable to its brevity and simplicity, production of **13** gives rise to an undesired side product **14**, which is difficult to remove by recrystallization or chromatography of the product mixture.

[0068] Accordingly, the invention provides a method of separating components of a mixture. The components of the mixture comprise a substituted-methylene quinone **13** and a quinone **14**. R^1 , R^2 , and R^3 can be independently selected from substituted or unsubstituted C_1 - C_6 alkyl groups. Z is halogen, preferably chlorine. This method comprises contacting the mixture with a reactive species that selectively binds through a heteroatom to the methylene carbon of said substituted-methylene quinone, displacing said leaving group, producing a charged substituted-methylene quinone, and separating the charged substituted-methylene quinone from the quinone, thus separating the mixture.

[0069] In an exemplary embodiment, the method further comprises contacting the substituted-methylene quinone with a vinylalane, under conditions appropriate to form a ubiquinone.

[0070] In another exemplary embodiment, the invention provides a method of separating components of a mixture. The components of the mixture comprise a substituted methylene quinone and a quinone having the formula:



respectively. R^1 , R^2 , and R^3 can be independently selected from substituted or unsubstituted C_1 - C_6 alkyl groups. Z is halogen, preferably chlorine. This method comprises contacting the mixture with a reactive species that selectively binds through a heteroatom to the methylene carbon of said substituted methylene quinone and displaces the halogen. In the following step, the substituted-methylene quinone is separated from the quinone, thus separating the mixture.

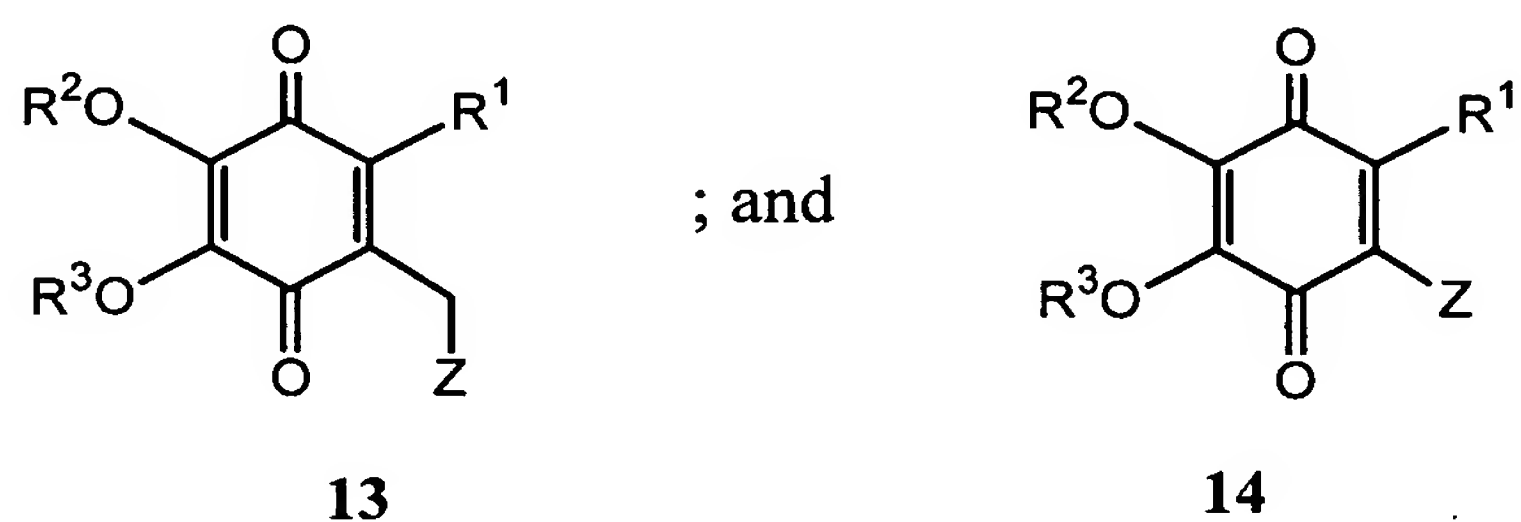
[0071] In an exemplary embodiment, the reactive species is a substituted or unsubstituted C_1 - C_{20} carboxylate. In another exemplary embodiment, the separating is by

chromatography. In another exemplary embodiment, the method further comprises contacting the substituted-methylene quinone with a vinylalane, under conditions appropriate to form a ubiquinone.

[0072] In another exemplary embodiment, the invention provides an alternate route to separating a reactive substituted-methylene quinone from an analogous substituted quinone by selectively changing the halogen on the substituted-methylene quinone to a leaving group that alters the polarity of the molecule and, optionally, allows it to be crystallized away from the quinone. Thus, in one embodiment, a halogen leaving group is replaced with a charged species, *e.g.*, $(R^9)_2S^+$ or $(R^9)_3P^+$. The marked increase in polarity of these species relative to their precursors and the quinone allow the product to be easily separated from the quinone. In exemplary cases, the charged species are solids and can be purified by crystallization.

[0073] Another method according to this embodiment relies on lowering the polarity or enhancing the hydrophobicity of the substituted-methylene quinone by converting the halogen into a species such as an ester, *e.g.*, a carboxylate of a fatty acid, benzoic acid, etc. The increase in hydrophobic character of the desired product facilitates its separation from the quinone by recognized separation techniques, *e.g.*, chromatography.

[0074] In another aspect, the invention provides a method of separating components of a mixture. The components of the mixture comprise a substituted-methylene quinone and a halo-quinone having the formulae:



in which R^1 , R^2 , and R^3 can be independently selected from substituted or unsubstituted C_1 - C_6 alkyl groups. Z is a halogen. This method comprises contacting the mixture with a reducing agent that selectively reduces the halo-quinone to a halo-hydroquinone. Next, the halo-hydroquinone is contacted with a base, forming an anion of the halo-hydroquinone. Next, the anion of the halo-hydroquinone is separated from the quinone, thereby separating the mixture.

[0075] In an exemplary embodiment, the method further comprises contacting the halomethylated quinone with a vinylalane, under conditions appropriate to form a ubiquinone. Other methods of forming ubiquinones are presented in the section entitled “Synthesis of the Products”.

[0076] In an exemplary embodiment, the mixture is contacted with a metal ion, generally used in the form of a salt or complex that preferentially reduces **14** to the corresponding hydroquinone. An exemplary metal ion is a transition metal ion, *e.g.*, Fe(II). Basic extraction removes the acidic hydroquinone from **13**.

[0077] The reducing agent, *e.g.*, the metal ion, is present in any useful quantity. It is well within the abilities of those of skill in the art to determine both the identity, *e.g.*, metal-containing compound, and an appropriate amount of the reducing agent for a particular purpose. For example, a vast array of data relevant to reduction and oxidation potentials of organic compounds and reducing agents, respectively, is available to those designing a purification strategy according to the instant invention.

[0078] In an exemplary embodiment, the reducing agent is a metal ion salt or complex that is sufficiently soluble in the solvent containing the desired quinone of the side product that it can be provided as a solution that is at least 0.01 mole%, preferably at least 0.05 mole%, more preferably, at least 0.1 mole%, and still more preferably, at least 0.5 mole%, in the metal ion. An exemplary species of use in the present invention is Mohr’s salt, $(\text{NH}_4)_2\text{Fe}(\text{SO}_4)_2$. Other iron salts and metal species able to selectively transfer an electron to a haloquinone are of use in the present invention.

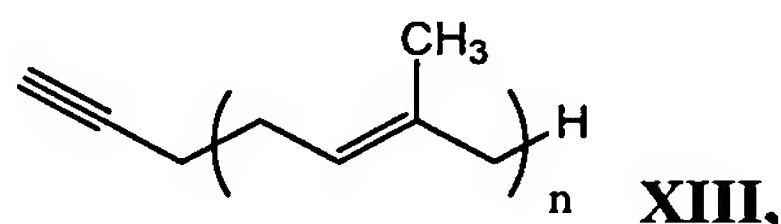
[0079] Alternatively, mixtures of **13** and **14** (**Fig. 4**) can be used directly in the coupling reaction according to the present invention. Chloromethylated quinone **13**, contaminated by the corresponding chloroquinone by-product **14**, can be used as a mixture of crude materials, preferably after quick filtration through a short plug of basic alumina to remove undesired components. The mixtures can for example contain up to about 50%, preferably about 0.5 to about 30% by weight of **14**, which is not reacting under the appropriate conditions for the coupling.

[0080] The species purified by the strategies set forth above can then be advanced to a coupling reaction with a carboaluminated species without the need for further modification.

Synthesis of the Carboaluminated Species

[0081] In another aspect, the invention provides a method of carboaluminating an alkyne substrate, preferably a terminal alkyne, thus forming a carboaluminated species with an alkyl moiety bound to aluminum. This method comprises contacting an alkyne substrate with a compound $(L)_{p+1}M$, wherein M is aluminum, and x equivalent of water, an alcohol $R^{20}OH$, or methylaluminoxane (MAO) relative to the alkyne substrate, thus carboaluminating the alkyne substrate. The symbol x can have a value between 0 to 1 ($0 < x < 1$). L can be a ligand independently selected from substituted or unsubstituted alkyl, alkoxy, aryl or aryloxy with 1 to 10 carbon atoms. The symbol p can be 1 or 2. In a preferred embodiment at least one of the ligands L is methyl. In a particularly preferred embodiment, $(L)_{p+1}M$ is $(Me)_3Al$. R^{20} is a branched or unbranched alkyl radical with 1 to 15 carbon atoms, which can be optionally substituted with 1 to 5 hydroxy substituents. Preferred alcohols $R^{20}OH$ include methanol, ethanol, propanol, isopropanol, *n*-butanol, *sec*-butanol, *tert*-butanol and the like.

[0082] In an exemplary embodiment, the carboaluminated species of the method (a compound of Formula IV, for example) is utilized in a subsequent coupling reaction to a substituted methylene moiety (eg. a compound of Formula II, for example, in which R^{5a} is CH_2OR^7 , or 13). In an exemplary embodiment, the alkyne substrate comprises a prenoidal moiety. In an exemplary embodiment, the alkyne substrate has the formula,



wherein n can be an integer from 0 to 19.

[0083] In another exemplary embodiment of the method for carboalumination according to the present invention, the water, the alcohol or methylaluminoxane (MAO) can be present in an amount from about 2-50 mol-% relative to said alkyne substrate.

[0084] In another exemplary embodiment, the method further comprises contacting the alkyne substrate with a carboalumination catalyst, in an amount less than one equivalent relative to the alkyne substrate. In an exemplary embodiment, the carboalumination catalyst can be a member selected from zirconium- and titanium-containing species.

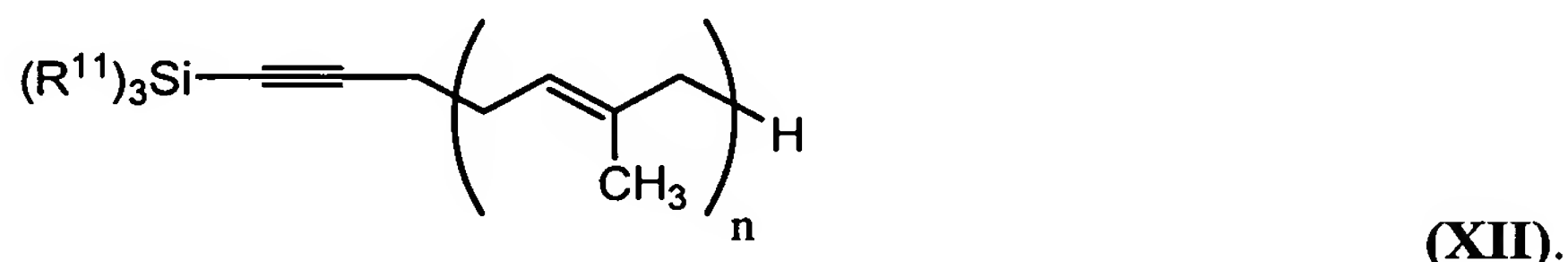
[0085] In another exemplary embodiment, the carboalumination can be in a solvent mixture of a chlorinated and a non-chlorinated solvent. In another exemplary embodiment, the carboalumination can be in a non-chlorinated solvent. Suitable non-chlorinated solvents

include hydrocarbons, e.g. hexanes, ligroin, toluene, petroleum ether. In a preferred embodiment, the carboalumination can be carried out in toluene or trifluoromethylbenzene or mixtures thereof.

[0086] In an exemplary embodiment, the alkyne substrate can be produced by a) forming a propyne dianion by contacting propyne with a base; and b) combining said propyne dianion with a compound according to Formula (X)



wherein Y^1 can be a leaving group, preferably halogen, e.g. chlorine, bromine or iodine, or sulfonic acid esters, e.g. tosylate or mesylate. s is an integer from 1 to 19. In an exemplary embodiment, the compound according to Formula (XII)



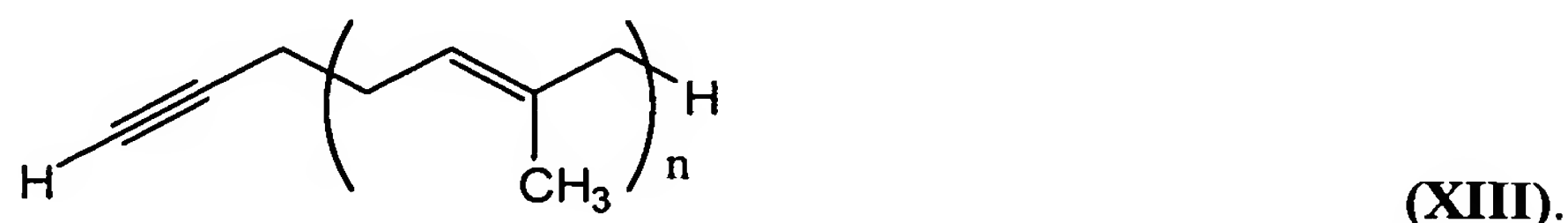
can be produced by a method comprising contacting a compound according to Formula (X) with an anion according to Formula (XI):



generated from $(R^{11})_3\text{SiC} \equiv \text{C} - \text{CH}_3$ in the presence of a base.

Anion (XI) is formed *in situ* or, alternatively, it is formed prior to combining it with a compound according to Formula (X). The anion is formed with an appropriate base, e.g., an organolithium base.

The compound according to Formula (XII) is subsequently desilylated, e.g. using an appropriate desilylation agent such as aqueous base, alkoxides and the like, to produce a compound according to Formula (XIII):



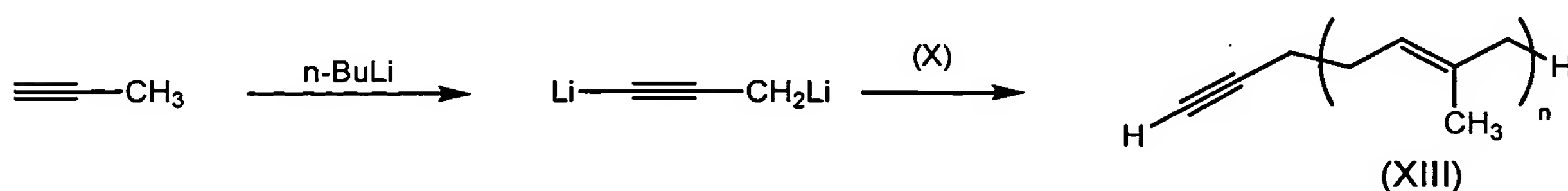
The compound of Formula (XIII) can then be carboaluminated to produce a compound according to Formula (IV).

[0087] In Formula (XI), groups represented by R^{11} include H, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, or a heteroatom bound to a group that satisfies the valency requirements of the heteroatom. Each R^{11} group is selected independently of the others; they may or may not be the same as the other R^{11} groups.

[0088] In another exemplary embodiment, the invention provides a method of carboaluminating an alkyne substrate having the formula (XIII), which comprises (a) contacting a reaction mixture comprising an alkyne substrate with an adsorbent medium; and (b) eluting the alkyne substrate from said adsorbent medium and collecting said alkyne substrate as a single fraction; and (c) submitting the product from step (b) to a carboaluminating reaction essentially without further purification, thus carboaluminating said alkyne substrate.

[0089] In an exemplary embodiment, the alkyne substrate is prepared using a derivative of solanesol and a reagent that adds a propyne synthon, *e.g.*, a silylated-propyne in metalated form, a propargyl Grignard reagent, or a dianion of propyne. The invention also provides a quick, efficient method of purifying an alkyne, such as those produced by the methods disclosed herein. The purification method includes dissolving the crude product from the reaction in an organic solvent, *e.g.*, petroleum ether, and passing the resulting solution through a short column of an adsorbent material, such as a chromatographic medium, *e.g.*, silica, alumina, and the like. The so purified alkyne substrate is sufficiently pure for use in the subsequent synthetic process, *e.g.* the said carboalumination, without a marked degradation in yield of, or quality of product produced by, the subsequent step.

[0090] In still a further exemplary embodiment, the invention provides a method of preparing the alkyne substrate according to Formula (XIII). In this method, a propyne dianion is formed by contacting propyne with a base, *e.g.*, *n*-butyllithium (*n*-BuLi), which is usually used in an amount of 2 to 15 equivalents. In an exemplary embodiment, the amount is of 2 to 8 equivalents, with respect to the propyne. The reaction is carried out at temperatures from -60 to 30°C. The dianion is then combined with a compound according to Formula (X).



[0091] The method of the invention using propyne gas has several advantageous features. For example, propyne gas is less expensive than TMS-propyne. Moreover, use of propyne eliminates the necessity for a desilylation step, providing a two-step protocol from propyne to the solanesyl alkyne. The use of the dianion also reduces side products commonly produced from the use of the TMS-propyne mono-anion (XI).

[0092] In another exemplary embodiment, the invention provides a method of carboalumination that utilizes a metal species, *e.g.*, a zirconium or titanium complex, in a catalytic quantity, which means in an amount of less than 1 molar equivalent relative to the alkyne substrate. Catalysts for this reaction are referred to herein as “carboalumination catalysts”. For example, the catalyst can be present in amounts of 0.1 to 20 mole %, preferably from about 0.5 to about 5.0 mole % relative to the alkyne. It has been discovered that minimizing the amount of zirconium species present does not have a deleterious effect on the efficiency of the carboalumination. Thus, the invention provides a method of carboalumination, using a catalytic amount of a metal species, *e.g.*, a zirconium or titanium species, that provides the carboaluminated species in high yields.

[0093] An exemplary carboalumination catalyst of use in the present invention is Cp_2ZrCl_2 . Those of skill in the art will recognize that numerous other metal-based catalysts, such as titanocenes and zirconocenes, are of use as carboalumination catalysts in the invention.

[0094] In this embodiment, the invention is based on recognition that the remaining organometallic carboalumination catalyst (*e.g.*, the zirconium salts), rather than the potential organic impurities, is problematic in the coupling of carboaluminated alkyne (IV) and a quinone (*e.g.* 13) to form a compound of Formula (III), and that minimization of the carboalumination catalyst allows for a shortened (“one pot”) route to the target ubiquinone. Thus, when a minimized amount of a zirconium or titanium species is used (*e.g.* ≤ 10 mole %), the carboaluminated product does not have to be separated prior to its being used in a coupling reaction with a quinone. Surprisingly, no marked degradation in the purity or quantity of the coupling product results from omitting the purification step.

[0095] The invention also provides an improved method for carboalumination of an alkyne substrate that utilizes both a catalytic amount of a carboalumination catalyst, *e.g.*, a zirconium or titanium species, and a catalytic amount of water, an alcohol (R^{20}OH as defined above) or methylaluminoxane (MAO), relative to the alkyne substrate.

[0096] In an exemplary embodiment, the carboalumination method of the invention utilizes less than stoichiometric amounts of water, alcohol ($R^{20}OH$ as defined above) or methylaluminoxane (*e.g.*, 1 - 25 mole % with respect to the alkyne), in conjunction with minimization of the carboalumination (*e.g.*, zirconocene) catalyst (*e.g.*, 1 - 10 mole % with respect to the alkyne), for which no literature precedent exists. Preferably less than 1, less than 0.75, less than 0.5, 0.4, 0.3, 0.2, or 0.01 equivalents of water, alcohol or methylaluminoxane are used. Under these new conditions, the carboalumination usually proceeds to completion. Recognized methods of carboalumination utilize a stoichiometric equivalent of water relative to the alkyne substrate. *See, for example, Wipf et al., Org. Lett.*, **2**: 1713-1716 (2000) or Negishi *et al.*, *Pure Appl. Chem.* **74**: 151-157 (2002).

[0097] The resulting vinyl alane, the reactivity of which towards carbon electrophiles is in large measure compromised when stoichiometric amounts of water are used, retains its reactivity under these novel conditions and can be used to generate the desired product (*e.g.* (III)) very cleanly upon reaction with a quinone (*e.g.* **13**) at $-20^{\circ}C$ in high yields, usually between 70-95%.

[0098] The aluminum present in the carboaluminated species, *e.g.* the one of Formula (IV) can be formally neutral (an alane) or it can be charged (an aluminate). The transition metal chemistry can be catalytic or stoichiometric. For example, the alkyne substrate can be aluminated by catalytic carboalumination, forming an adduct used directly in the synthesis of a ubiquinone or, alternatively, the metalated species is transmetalated to a different reagent.

[0099] The coordination number of M is satisfied by the bonding or coordination to the metal center of the requisite number of organic ligands or substituents, such as Lewis base donors (*e.g.*, halogen donors, oxygen donors, mercaptide ligands, nitrogen donors, phosphorus donors, and heteroaryl groups); hydrides; carbon ligands bound principally by σ -bonds (*e.g.*, alkyls, aryls, vinyls, acyl and related ligands); carbon ligands bound by σ - and π -bonds (*e.g.*, carbonyl complexes, thiocarbonyl, selenocarbonyl, tellurocarbonyl, carbenes, carbynes, σ -bonded acetylides, cyanide complexes, and isocyanide complexes); ligands bound through more than one atom (*e.g.*, olefin complexes, ketone complexes, acetylene complexes, arene complexes, cyclopentadienyl complexes, π -allyl complexes); unsaturated nitrogen ligands (*e.g.*, macrocyclic imines, dinitrogen complexes, nitric oxide complexes, diazonium complexes); and dioxygen complexes. Other useful combinations of metal ions

and ligands will be apparent to those of skill in the art. See, for example, Collman *et al.* PRINCIPLES AND APPLICATIONS OF ORGANOTRANSITION METAL CHEMISTRY, University Science Books, 1987.

[0100] In another exemplary embodiment, the invention provides a method of carboaluminating an alkyne substrate, *e.g.*, a terminal alkyne. The method includes contacting the alkyne substrate with a compound of the formula $(L)_{p+1}M$, wherein L, p and M are defined as above, *e.g.* $(Me)_3Al$, in an amount of 1 to 10 equivalents, preferably in an amount from 1 to 5 equivalents, especially in an amount from 1 to 2.5 equivalents, and most preferably from 1.3 to 1.8 equivalents, relative to the alkyne substrate, in the presence of less than one equivalent of water, an alcohol $R^{20}OH$, or alkylaluminumoxane (*e.g.*, methylaluminumoxane (methyl aluminum oxide) $[-Al(CH_3)O-]_n$) relative to the alkyne substrate.

[0101] The order of addition of reactants for carrying out the method of carboalumination according to the present invention can also be varied. In an exemplary embodiment, the carboalumination catalyst and metal compound $(L)_{p+1}M$ are contacted first and the alkyne substrate is subsequently added, followed by water, an alcohol ($R^{20}OH$) or methylaluminumoxane (MAO). In an exemplary embodiment, the carboalumination catalyst and alkyne substrate are contacted first and the metal compound added subsequently, followed by the water, an alcohol ($R^{20}OH$) or methylaluminumoxane (MAO). In an exemplary embodiment, the alkyne substrate and metal compound are contacted first and the carboalumination catalyst subsequently added, followed by water, an alcohol ($R^{20}OH$) or methylaluminumoxane (MAO). In another exemplary embodiment, the metal compound and water, an alcohol ($R^{20}OH$) or methylaluminumoxane (MAO) are added together and the alkyne substrate added subsequently, followed by the carboalumination catalyst.

[0102] The present invention can be conducted under a variety of conditions. For example, the carboalumination reaction can be conducted at a temperature from about $-40^{\circ}C$ to about $50^{\circ}C$. In an exemplary embodiment, the temperature of the carboalumination reaction can be at about room temperature. In another exemplary embodiment, the temperature of the carboalumination reaction can be from about $-20^{\circ}C$ to about $20^{\circ}C$. In another exemplary embodiment, the temperature of the carboalumination reaction can be from about $-10^{\circ}C$ to about $12^{\circ}C$.

[0103] The length of time for the carboalumination reaction can vary from 30 minutes to 100 hours. In general, the lower the temperature at which the reaction is conducted, the longer the amount of time for the reaction to go to completion. For example, when the temperature is room temperature, the reaction can be completed from 9 hours to 12 hours. When the temperature is 0°C, the reaction can be completed from 19 hours to 25 hours.

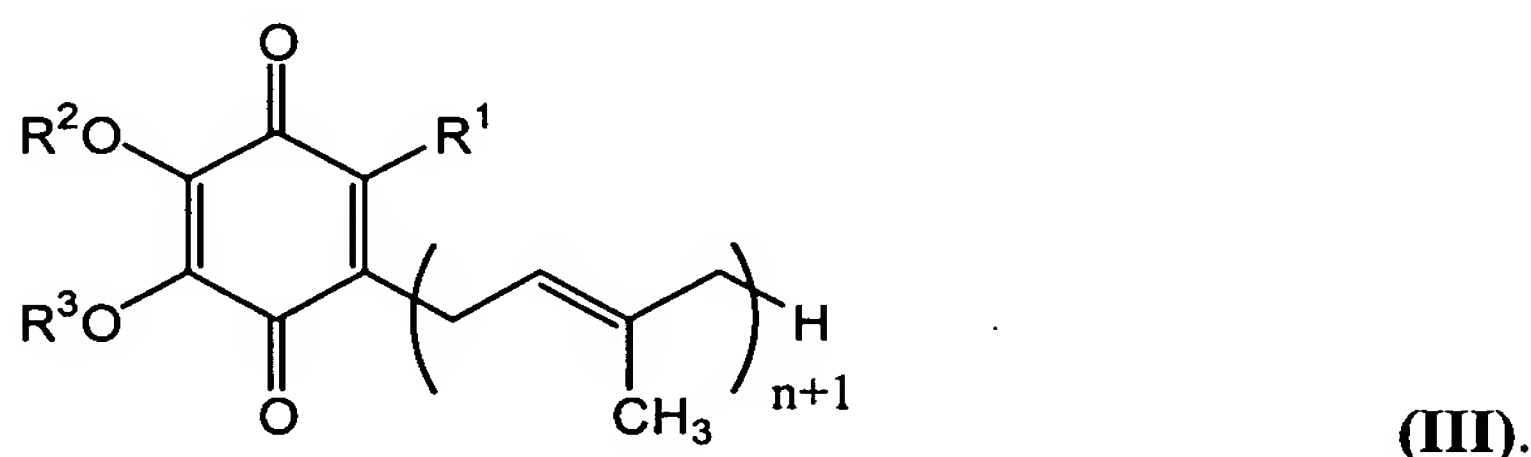
[0104] The present invention also provides an unprecedented method of carboalumination utilizing solvents that are more “environmentally friendly” than art-recognized methods using halogenated solvents, *e.g.*, dichloroethane. For example, in one embodiment, the invention provides a method of carboalumination that occurs in a solvent that includes at least one hydrocarbon (hexanes, ligroin, toluene, petroleum ether), *e.g.*, an aromatic hydrocarbon, other than a chlorinated hydrocarbon. The solvent can be devoid of chlorinated hydrocarbons or the chlorinated solvents can be used in admixture with a solvent with less deleterious properties. Reducing or eliminating the use of halogenated solvents is a significant advance in the art.

[0105] The present method also provides an advanced approach for processing the alkyne substrate precursor to the CoQ_{n+1} side-chain. The present method is analogous to the method of preparing the terminal alkyne set forth in U.S. Patent No. 6,545,184. The method of the invention simplifies purification of the crude alkyne substrate (XIII) obtained, following standard workup, by filtration of the crude material through a small amount of a chromatographic medium, using an organic solvent of low polarity, *e.g.*, petroleum ether, hexanes, etc., to elute the alkyne substrate from the medium. Importantly, the method obviates the need to fractionate the alkyne substrate, which elutes off the medium and is collected as a single fraction that contains essentially all of the small molecular organic species. An exemplary medium is a small plug of sand with an equal volume of adsorbent such as silica gel. Removal of the solvent leaves colorless to pale yellow material of *ca.* 70-80% purity that is ready to be used directly in the next step involving carboalumination. The purity of the material used to prepare the alkyne substrate is not critical and can be varied over a broad range of about 10-99% by weight. Material of lower purity will afford an alkyne substrate of lower purity. It was not recognized previously that use in a carboalumination of a crude alkyne substrate preparation, having only inorganics and highly polar organics removed, could provide material as pure and in as good of a yield as the use of a highly purified alkyne substrate, *e.g.*, chromatographically purified. Alternatively, purified alkyne substrate can be used in the carboalumination.

Synthesis of the Products

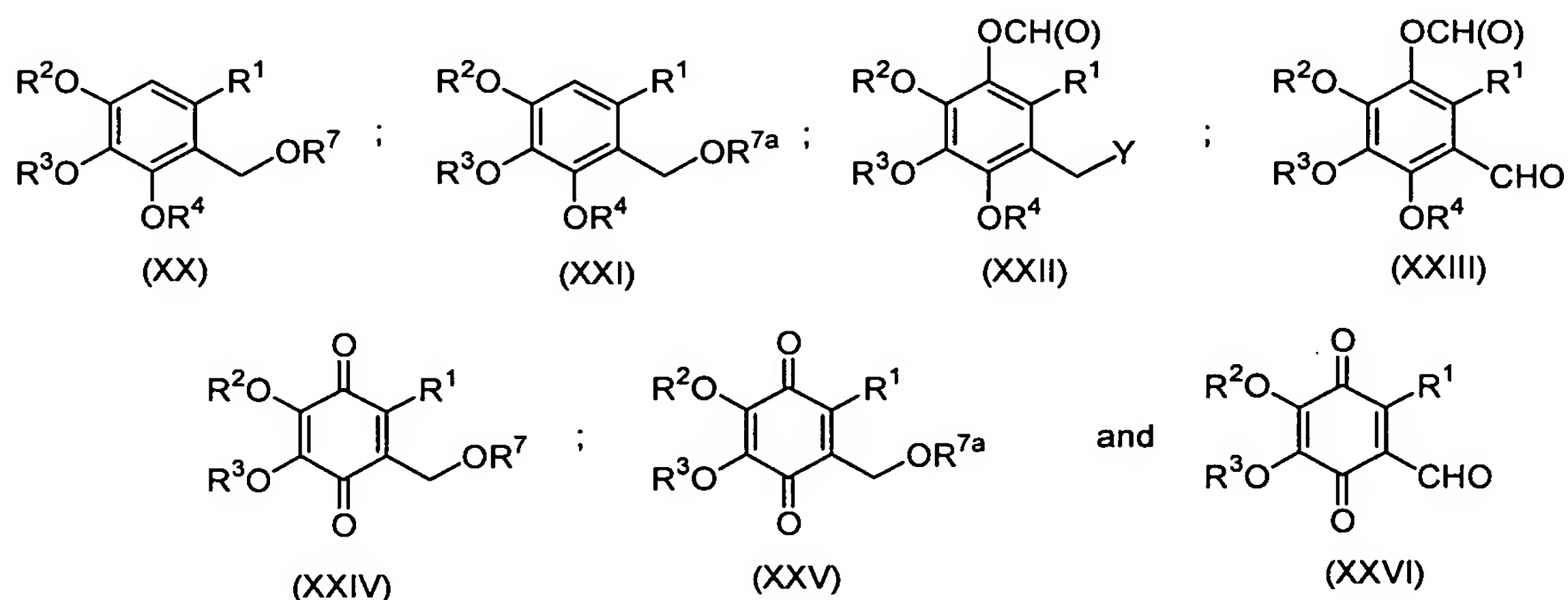
[0106] In one aspect, the method of the present invention is based on a retrosynthetic disconnection that relies on the well-known maintenance of olefin geometry in group 10 transition metal coupling reactions (Hegedus, TRANSITION METALS IN THE SYNTHESIS OF COMPLEX ORGANIC MOLECULES, University Science Books, Mill Valley, CA, 1994). The discussion that follows focuses on a reaction, in which the coupling partners are a vinyl organometallic and a substituted-methylene quinone in which the methylene group is substituted with a leaving group (*e.g.*, halomethyl quinone, ether, sulfonate, etc.). Please note that these reactions have similarities to coupling reactions between a vinyl alane and a protected, substituted-methylene phenol, as described in U.S. Pat. No. 6,545,184, which is herein incorporated by reference. The focus of the discussion is for clarity of illustration, and other methods and coupling partners appropriate for use in those methods will be apparent to those of skill in the art and are within the scope of the present invention.

[0107] Thus, the present invention provides a method for preparing a compound according to Formula (III):

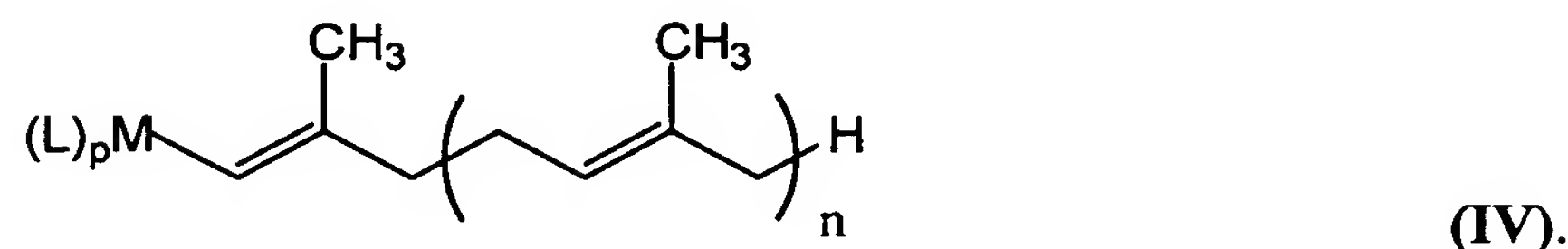


In Formula (III), each of R^1 , R^2 , R^3 and n is as described above.

[0108] In one aspect, the method of the invention comprises, contacting one or more of the following substituted-methylene moieties:



in which the substituents are as discussed above, with a carboaluminated species according to Formula (IV).



In Formula (IV), L, p, n and M are defined as above. The coupling takes place in the presence of a coupling catalyst that is effective at catalyzing coupling between the methylene carbon atom on the aromatic group or of the quinone moiety mentioned above, and the vinylic carbon attached to M on the compound according to Formula (IV).

[0109] In one embodiment of the invention compounds **7** or **8** and a compound according to Formula (IV) can be contacted in the presence of a coupling catalyst that is effective at catalyzing the coupling of the methylene carbon of a substituted methylene moiety, such as that in compounds **7** and **8**, and a carboaluminated species, such as that according to Formula (IV). The coupling of compound **7** or **8** with a compound according to Formula (IV) affords the compound according to Formula (III). A representative example for preparing a ubiquinone, starting with quinone **7** or **8** (**FIG. 1**) is set forth in **FIG. 2**.

[0110] In a particularly preferred embodiment, a compound of formula **13** (e.g. compound **8**) is contacted with a compound of formula (IV) derived from the carboalumination method as described above.

Particular preference is given to a carboalumination process, that is conducted in the presence of substoichiometric amounts of water, an alcohol ($R^{20}OH$) or methylaluminoxane (MAO), and in the presence of about 0.5 to 20 mole % of a coupling catalyst (e.g. a zirconium or titanium species as described above). Preferably the subsequent coupling reaction is carried without prior removal of the carboalumination catalyst or the species derived thereof from the resulting vinyl alane. This allows to conduct the carboalumination and the subsequent coupling as a “one pot” reaction, i.e. a reaction that is conducted in one vessel. The present methodology offers a convenient access to Coenzyme Q_{10} , which is the particularly preferred product of the methods according to this invention. The methodology offers the advantage of applicability to a technical scale.

[0111] In another exemplary embodiment, the coupling catalyst utilizes a species that comprises a transition metal. Exemplary transition metal species of use as coupling catalysts include, but are not limited to, those metals in Groups IX, X, and XI. Exemplary metals

within those Groups include Cu(I), Pd(0), Co(0) and Ni(0). Recent reports have demonstrated that catalyst couplings, using the appropriate reaction partners and based on metal catalysis, are quite general and can be used to directly afford known precursors (Naruta, *J. Org. Chem.*, **45**:4097 (1980); Eren, *et al.*, *J. Am. Chem. Soc.*, **110**:4356 (1988) and references therein; Van Lient *et al.*, *Rec. Trav. Chim. Pays-Bays* **113**:153 (1994); Rüttiman *et al.*, *Helv. Chim. Acta*, **73**:790 (1990); Terao *et al.*, *J. Chem. Soc., Perkin Trans. 1*:1101 (1978), Lipshutz *et al.*, *J. Am. Chem. Soc.* **121**: 11664-11673 (1999); Lipshutz *et al.*, *J. Am. Chem. Soc.* **118**: 5512-5313 (1999)). In another exemplary embodiment, the metal is Ni(0).

[0112] The coupling catalyst can be formed by any of a variety of methods recognized in the art. In an exemplary embodiment in which the transition metal is Ni(0), the coupling catalyst is formed by contacting a Ni(II) compound with two equivalents of a reducing agent, reducing Ni(II) to Ni(0). In an exemplary embodiment, the Ni(II) compound is NiCl₂(PPh₃)₂. In yet another exemplary embodiment, the reducing agent is n-butyllithium. In yet another exemplary embodiment, the method of the invention comprises contacting NiCl₂(PPh₃)₂, or a similar Ni species, with about two equivalents of a reducing agent (*e.g.*, n-butyllithium), thereby reducing said NiCl₂(PPh₃)₂ to Ni(0). Alternatively, other readily available forms of Ni(0) can be employed (*e.g.*, Ni(COD)₂).

[0113] The coupling catalyst can be a homogeneous or heterogeneous catalyst (Cornils B, Herrmann WA, APPLIED HOMOGENEOUS CATALYSIS WITH ORGANOMETALLIC COMPOUNDS: A COMPREHENSIVE HANDBOOK IN TWO VOLUMES, John Wiley and Sons, 1996; Clark JH, CATALYSIS OF ORGANIC REACTIONS BY SUPPORTED INORGANIC REAGENTS, VCH Publishers, 1994; Stiles AB, CATALYST SUPPORTS AND SUPPORTED CATALYSTS: THEORETICAL AND APPLIED CONCEPTS, Butterworth-Heinemann, 1987). In one exemplary embodiment, the coupling catalyst is supported on a solid material (*e.g.*, charcoal, silica, *etc.*). In another exemplary embodiment, the coupling catalyst is a supported nickel catalyst (*see, e.g.*, Lipshutz *et al.*, *Synthesis*, 2110 (2002); Lipshutz *et al.*, *Tetrahedron* **56**:2139-2144 (2000); Lipshutz and Blomgren, *J. Am. Chem. Soc.* **121**: 5819-5820 (1999); and Lipshutz *et al.*, *Inorganica Chimica Acta* **296**: 164-169 (1999)).

[0114] The method of the invention is practiced with any useful amount of coupling catalyst effective at catalyzing coupling between the methylene carbon atom on the aromatic group or of the quinone moiety mentioned above, and the vinylic carbon attached to M on

the compound according to Formula (IV). In an exemplary embodiment, the coupling catalyst is present in an amount from about 0.1 mole % to about 10 mole %. In an exemplary embodiment, the coupling catalyst is present in an amount from about 0.5 mole % to about 5 mole %. In an exemplary embodiment, the coupling catalyst is present in an amount from about 2 mole % to about 5 mole %.

[0115] The above mentioned coupling reaction can be carried out in all solvents known to those of skill in the art, suitable as solvents for transition metal catalyzed coupling reactions, e.g. ethers e.g. THF, diethyl ether and dioxane, amines e.g. triethylamine, pyridine and NMI, and others e.g. acetonitrile, acetone, ethyl acetate, DMA, DMSO, NMP and DMF. In a preferred embodiment, it is not required to completely remove the solvent in which the carboalumination was carried out, prior to the coupling.

[0116] In FIG. 2, the quinone ether 7 or the chloromethyl quinone 8 is contacted with a vinylalane in the presence of a Ni(0) catalyst. The vinyl carbon attached to M in Formula (IV) and the methylene carbon of the quinone couple, affording the corresponding ubiquinone.

[0117] The conditions of the coupling reaction can be varied. For example, the order of addition of reactants can be varied. In an exemplary embodiment, the substituted methylene moiety and carboaluminated species are contacted, and then the coupling catalyst is subsequently added. In an exemplary embodiment, the substituted methylene moiety and coupling catalyst are contacted, and then the carboaluminated species is subsequently added. In an exemplary embodiment, the coupling catalyst and carboaluminated species are contacted, and then the substituted methylene moiety is subsequently added.

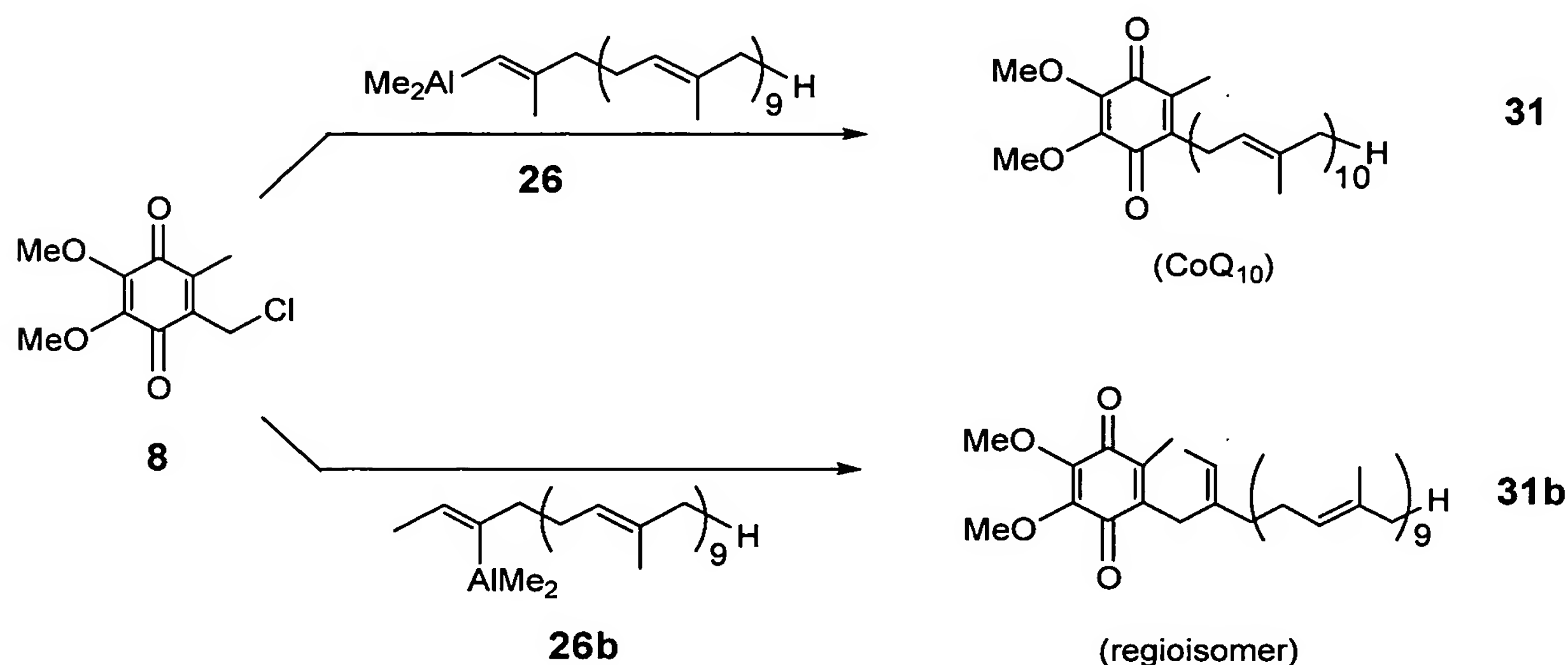
[0118] The amount of the substituted methylene moiety relative to the alkyne employed in the prior carboalumination can also be varied. In an exemplary embodiment, the substituted methylene moiety, e.g. compound 8, can be reacted in amounts ranging from 0.9 to 10 equivalents relative to the alkyne mentioned above. In another exemplary embodiment, the substituted methylene moiety can be reacted in amounts ranging from 0.9 to 5 equivalents, preferably from 0.9 to 2, and most preferably from 1.1 to 1.6 equivalents, relative to the alkyne mentioned above.

[0119] The coupling reaction of the present invention can be conducted under a variety of conditions. For example, the coupling reaction can be conducted at a temperature from –40°C to 50°C. In an exemplary embodiment, the temperature of the coupling reaction can

be room temperature. In another exemplary embodiment, the temperature of the carboalumination reaction can be from $-30\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$. In another exemplary embodiment, the temperature of the carboalumination reaction can be from about $-25\text{ }^{\circ}\text{C}$ to about $-15\text{ }^{\circ}\text{C}$.

[0120] The length of time for the coupling reaction can vary from 10 minutes to 10 hours. In general, the lower the temperature at which the reaction is conducted, the longer the amount of time for the reaction to go to completion. When the temperature is about $0\text{ }^{\circ}\text{C}$, the reaction can be completed from 30 minutes to 3 hours.

[0121] The carboalumination reaction can yield mixtures of regioisomeric vinyl alanes **26** and **26b**, which in turn lead to mixtures of CoQ₁₀ (**31**) and its regioisomer (**31b**) in the subsequent coupling with the methylene carbon of chloromethylated quinone **8** as shown below. The factors influencing the regioselectivity of the carboalumination are well known to those skilled in the art. Those include for example the temperature, the nature of the solvent and of the carboalumination catalyst.



Further processing after coupling

[0122] The substituted methylene moiety synthesized by the method of the invention is generally oxidized to the corresponding quinone, if the moiety was not already a quinone. The phenol can be oxidized directly to the quinone or, alternatively, it can first be converted to the corresponding hydroquinone and oxidized to the quinone. An array of reagents and reaction conditions are known that oxidize phenols to quinones, *see*, for example, Trost BM *et al.* COMPREHENSIVE ORGANIC SYNTHESIS: OXIDATION, Pergamon Press, 1992.

[0123] In an exemplary embodiment, the oxidant comprises a transition metal chelate. The chelate is preferably present in the reaction mixture in an amount from about 0.1 mole % to about 10 mole %. In another exemplary embodiment, the transition metal chelate is used in conjunction with an organic base, such as an amine. Exemplary amines are the trialkyl amines, such as triethylamine. In another exemplary embodiment, the transition metal chelate is Co(salen). The chelate can be a heterogeneous or homogeneous oxidant. In an exemplary embodiment, the chelate is a supported reagent.

[0124] Alternate synthetic routes for use converting the compounds of the invention to ubiquinones, and methods to prepare useful intermediates, are provided in U.S. Patent No. 6,545,184 to Lipshutz *et al.*, the disclosure of which is herein incorporated by reference.

[0125] The materials, methods and devices of the present invention are further illustrated by the examples that follow. These examples are offered to illustrate, but not to limit the claimed invention.

EXAMPLES

General

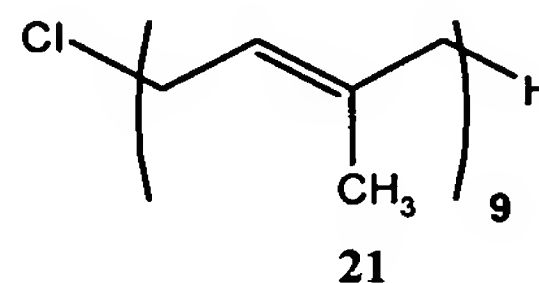
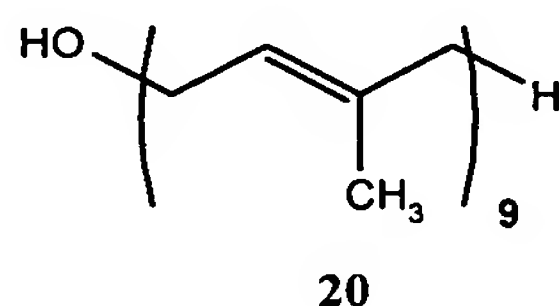
[0126] In the examples below, unless otherwise stated, temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, “rt,” or “RT,” (typically a range of from about 18-25 °C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (typically, 4.5-30 mm Hg) with a bath temperature of up to 60 °C; the course of reactions was typically followed by thin layer chromatography (TLC) and reaction times are provided for illustration only; melting points are uncorrected; products exhibited satisfactory ¹H-NMR and/or microanalytical data; yields are provided for illustration only; and the following conventional abbreviations are also used: mp (melting point), L (liter(s)), mL (milliliters), mmol (millimoles), g (grams), mg (milligrams), min (minutes), h (hours), RBF (round bottom flask).

[0127] The following chemicals were subjected to the following preparatory steps prior to use in the Examples. PCl₃ was refluxed for 3 h at 76 °C while slowly purging with dry argon to expel HCl, distilled at atmospheric pressure and stored in a sealed container under argon until needed. DMF, 2-propanol and benzene were used as supplied from Fisher chemicals. Solanesol, purified by column chromatography on SiO₂ with 10% diethyl ether/petroleum ether, was dried azeotropically with toluene or benzene immediately prior to

use. THF was distilled from Na/benzophenone ketyl prior to use. *n*-BuLi was obtained as a 2.5 M solution in hexanes from Aldrich and standardized by titration immediately prior to use. Ethanol was 200 proof, dehydrated, U.S.P. Punctilious grade. All other reagents were purchased from suppliers and used without further purification. Products were confirmed by ^1H NMR, ^{13}C NMR, IR, LREIMS and HR-EI or HR-CI Mass Spectrometry. TLC and chromatographic solvents are abbreviated as follows: EA: ethyl acetate; PE: petroleum ether; DCM: dichloromethane.

EXAMPLE 1

1.1 Production of 21: Chlorination of Solanesol



[0128] PCl_3 (180 μL , 2.10 mmol) and DMF (110 μL , 2.10 mmol) were added to a 25 mL pear-shaped flask and stirred slowly at RT for 10 min until the solution solidified into a white solid. Solanesol, **20** (2.20 g, 3.50 mmol) was dissolved in 7.0 mL THF and added *via* cannula to the PCl_3 /DMF reagent. The heterogeneous reaction was stirred at RT for 2 h, and then the solvent was completely removed *in vacuo* to produce a yellow oil. Absolute ethanol (10.0 mL) was added and the flask agitated. The white precipitate was filtered to yield 2.16 g (95.1%) solanesyl chloride, **21**.

1.2 Alternative Production of 21: Chlorination of Solanesol

[0129] 40 g (58.4 mmol) water free solanesol, **20** (purity 92 % by weight) was dissolved in 158 mL (646 mmol) CCl_4 and 30.6 g (0.1168 mmol) triphenylphosphine was added at 20 – 25 $^\circ\text{C}$. The solution was heated to reflux for 6 h. After that additional 3.1 g (0.012 mmol) of triphenylphosphine was added. The solution was refluxed for 1 h and then stirred at RT for 12 h.

[0130] The resulting suspension was diluted with 125 mL *n*-heptane and filtered through a sintered glass filter. The resulting solution was concentrated *in vacuo* to remove excess CCl_4 , and the resulting brown viscous residue redissolved in 125 mL *n*-heptane, washed 3 times with a 60:40 (v/v) mixture of methanol and water (once 62 mL, then 2 times 31 mL).

A solution of brine (62 mL) was added to the combined methanolic extracts, which were extracted with heptane (62 mL). The heptane layer was separated, washed twice with a 60:40 (v/v) mixture of methanol and water (twice 32 mL). The combined heptane phases were dried over sodium sulphate, filtered and evaporated, yielding 31.2 g of a brown liquid containing 93% weight-% of solanesyl chloride, **21** (yield: 76.2%).

1.3 Alternative Production of 21: Chlorination of Solanesol

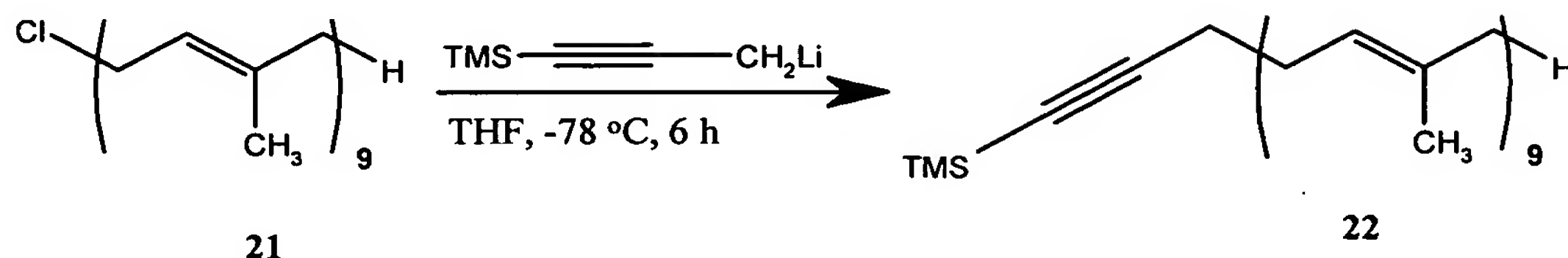
[0131] 23.9 g (30 mmol) of crude solanesol, **20** (purity: 79% by weight) was contacted with acetonitrile (71 mL) (biphasic mixture), 9.2 g (60 mmol) CCl₄ and 15.7 g (60 mmol) of triphenylphosphine were added. The mixture was heated to reflux for 1 h after which time TLC analysis shows complete conversion. The mixture was kept at reflux for 4 h. The reaction mixture was then extracted 3 times with n-heptane (50 mL each). The combined organic extracts were washed twice with a 60:40 (v/v) mixture of methanol and water (50 mL each) and then with brine and dried over sodium sulphate. The solvent was removed under reduced pressure to afford 22.9 g of a brown liquid containing 60.3 weight-% solanesyl chloride, **21** (yield: 71.0%).

1.4 Alternative Production of 21: Chlorination of Solanesol

[0132] 23.9 g (30 mmol) of crude solanesol, **20** (purity: 79% by weight) was dissolved in THF (71 mL) and 9.2 g (60 mmol) CCl₄ and 15.7 g (60 mmol) of triphenylphosphine were added. The clear solution was heated to reflux for 6 h after which time TLC analysis showed complete conversion. n-Heptane (63 mL) was added to the reaction mixture and the suspension filtered over a sintered glass frit (por. 3). The filter cake was washed with n-heptane (30 mL). The organic filtrate was washed 3 times with a 60:40 (v/v) mixture of methanol and water (30 mL each) and then with brine and dried over sodium sulphate. The solvent was removed under reduced pressure to afford 17.8 g of a brown liquid containing 80.6 weight-% solanesyl chloride, **21** (yield 73.9%).

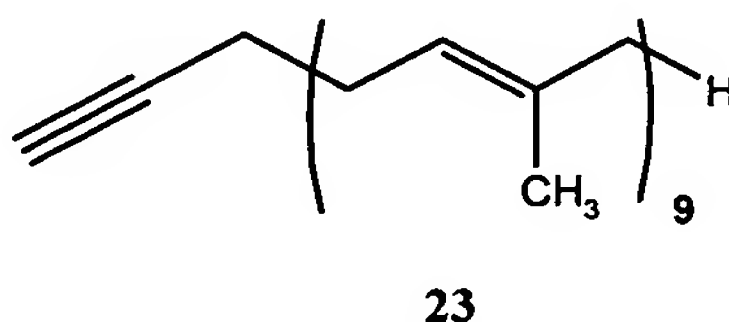
EXAMPLE 2

2.1 *Alkylation of Lithiated Propyne*



[0133] THF (4.7 mL) at -40 °C was charged with 0.36 mL *n*-BuLi (2.51 M in hexanes, 0.90 mmol) and after 5 min, 170 μ L TMS-propyne (129 mg, 1.16 mmol) were added. After 0.75 h at -40 °C, the reaction was cooled to -78 °C. Crude **21** (629 mg, 0.97 mmol) dissolved in 5 mL THF was cooled to -78 °C and added slowly *via* cold cannula. The reaction was stirred at -78 °C for 6 h and quenched by addition of 1 mL saturated NH_4Cl solution, and the brownish-yellow mixture concentrated *via* rotary evaporation to a yellow oil. The residue was partitioned between 10 mL water and 10 mL petroleum ether and the layers separated. The aqueous phase was extracted 3 x 10 mL petroleum ether and the combined organic extracts washed with 10 mL brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (0.5% CH_2Cl_2 /petroleum ether) gave the product, **22**, as a clear, colorless oil which solidified upon standing (611 mg; 87%).

2.2 *Deprotection of the Alkyne 22*



[0134] Ethanol (15 mL, 190 proof) was treated with 53 mg (2.30 mmol) freshly cut $\text{Na}(0)$. After all solid $\text{Na}(0)$ had dissolved, 2.76 mL of the sodium ethoxide solution (0.154 M in NaOEt , 0.43 mmol) was added to 250 mg TMS-protected alkyne substrate, **22** (0.245 mmol). A reflux condenser was attached and the reaction mixture heated to 60 °C for 4 h. Petroleum ether (10 mL) and water (10 mL) were then added, the layers separated and the aqueous layer extracted 3 x 10 mL petroleum ether. The combined organics were washed with 10 mL brine, dried over Na_2SO_4 and concentrated to a brown oil *via* rotary evaporation.

Flash chromatography with 5% CH₂Cl₂/ petroleum ether gave the terminal alkyne **23** (228 mg, 99%).

2.3 *Alternative Synthesis of 23*

[0135] A solution of n-butyllithium (30 mL, 75 mmol, 2.5M in hexanes, 3.75 eq) was added slowly to dry THF (60 mL), and then cooled to -7 °C. Gaseous propyne (670 mL, 30 mmol, 1.5 eq) was added at -7 °C. After complete addition of the propyne gas, the mixture was stirred for 1 h at -5 to 0 °C, warmed to RT and stirred at that temperature for further 80 min.

[0136] A solution of solanesyl chloride, **21**, (purity 75.5% by weight, 17.3 g, 20 mmol, 1.0 eq) in THF (80 mL) was then added dropwise to the aforementioned solution at temperatures between 0 and 2 °C. The reaction mixture was then stirred at 0 °C for 90 min and then poured into aqueous NH₄Cl solution. The organic phase was separated, the water phase was washed once with ethyl acetate (60 mL), the combined organic phases were washed with brine, and then dried over sodium sulphate. After removal of the solvents under reduced pressure 17.6 g of a light brown oil was obtained, containing 60.0 % weight-% of solanesyl alkyne substrate, **23** (yield: 80.9%).

2.4 *Alternative Synthesis of 23*

[0137] A solution of n-butyllithium (24 mL, 60 mmol, 2.5M in hexanes, 3.0 eq) was added slowly to dry THF (50 mL) at -40 °C. Gaseous propyne (670 mL, 30 mmol, 1.5 eq) was gassed in at -40 °C. After complete addition of the propyne gas, the cooling bath was removed and the mixture allowed to warm to 0 °C, at which temperature it was stirred for additional 3 h.

[0138] A solution of solanesyl chloride, **21** (purity 92.8% by weight, 14.0 g, 20 mmol, 1.0 eq) in THF (60 mL) was then added dropwise to the aforementioned solution at temperatures between 0 and 5 °C. The reaction mixture was then stirred at 0 °C for 2.5 h and then poured into aqueous NH₄Cl solution. The organic phase was separated, the water phase was washed once with ethyl acetate (50 mL), the combined organic phases were washed with brine and dried over sodium sulphate. After solvent evaporation under reduced pressure 13.8 g of a light brown oil was obtained, containing 71.8 % weight-% of solanesyl alkyne, **23** (yield: 76.0%).

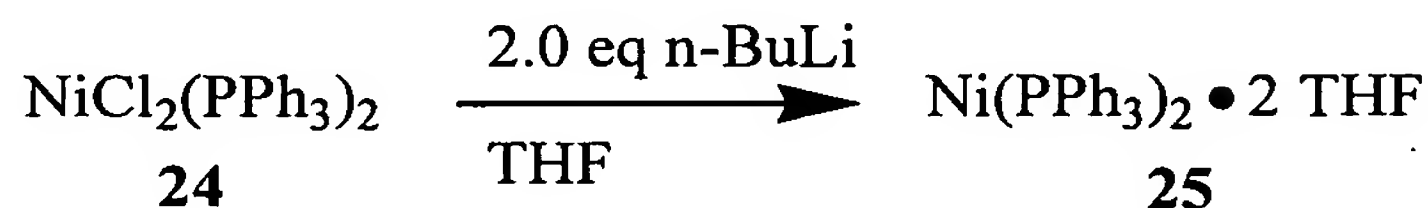
2.5 Alternative Synthesis of 23

[0139] A solution of *n*-butyllithium (30 mL, 75 mmol, 2.5M in hexanes, 6.25 eq) was added slowly to dry THF (60 mL) at -40°C . Propyne gas (670 mL, 30 mmol, 2.5 eq) was added to the mixture at -40°C . After complete addition of the propyne gas, the cooling bath was removed and the mixture allowed to warm to 0°C , at which temperature it is stirred for 1 h. The suspension was then warmed to RT in 30 min and stirred for 1 h at RT.

[0140] The aforementioned suspension was cooled again to -20°C - -25°C , and a solution of solanesyl chloride, **21** (purity 75.5% by weight, 10.24 g, 11,8 mmol, 1.0 eq) in THF (50 mL) was then added dropwise to the aforementioned solution in the same temperature interval. The reaction mixture was then stirred for 1.5 h at temperatures from -25°C to -10°C . At -10°C , the mixture was poured into aqueous NH_4Cl solution. The organic phase was separated, the water phase was washed once with ethyl acetate (50 mL), the combined organic phases were washed with brine and dried over sodium sulphate. After solvent evaporation under reduced pressure 10.5 g of a light brown oil was obtained, containing 76.2% weight-% of solanesyl alkyne, **23** (yield: 83.0%).

EXAMPLE 3

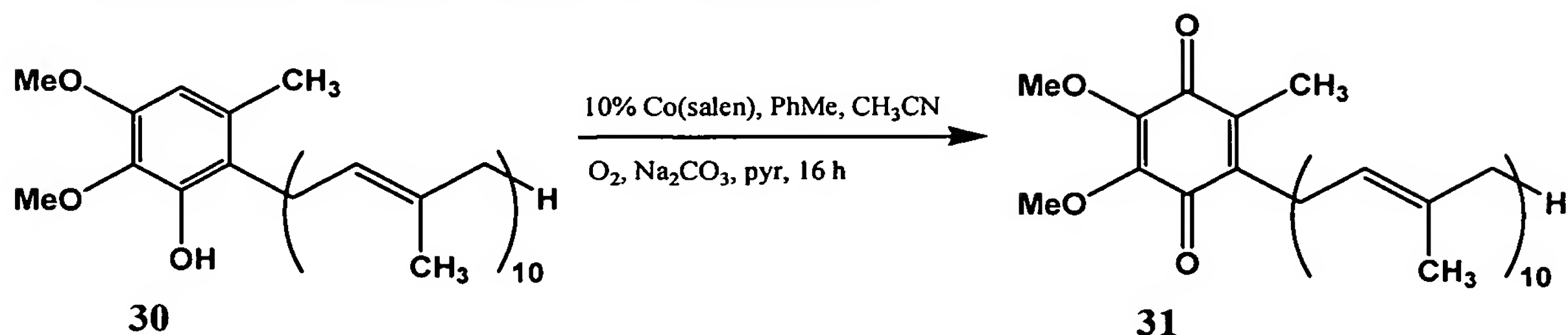
3.1 Preparation of the Ni(0) catalyst 25



[0141] In an oven dried 5 mL round bottomed flask containing a stir bar, cooled and purged with argon, was added **24**, $\text{NiCl}_2(\text{PPh}_3)_2$ (19.6 mg, 0.03 mmol) and the vessel was purged with argon for 2 min. THF (0.5 mL) was then added and slow stirring commenced. Slow addition of *n*-BuLi (0.026 mL, 0.058 mmol) gave a blood-red/black heterogeneous solution comprising **25** which was allowed to stir for 2 min prior to using it in the coupling reaction.

EXAMPLE 4

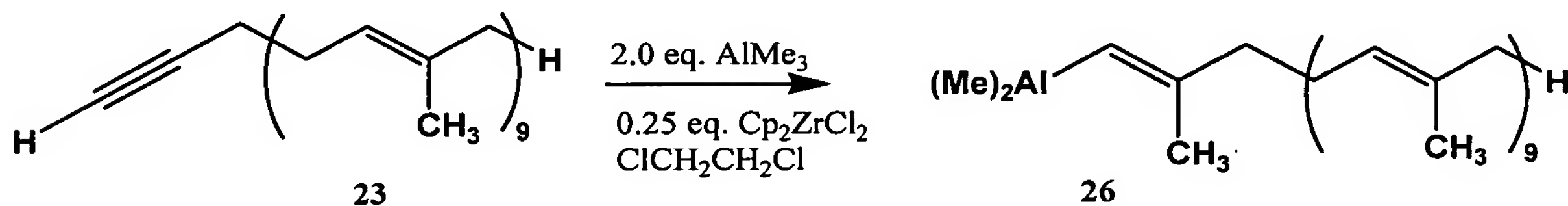
4.1 Oxidation of Prenoidal Phenol 30 to Quinone 31



[0142] In a clean 25 mL round bottom flask and stir bar (note: not oven dried and not under argon) the phenol 30 (99.4 mg, 0.117 mmol) was dissolved in toluene (1 mL) and Na₂CO₃ (36.4 mg, 0.37 mmol) and pyridine (1 μ L, 0.012 mmol) were added. Co(salen) (1.9 mg, 0.006 mmol) was then added as a red-purple solid and the reaction vessel was purged with ~0.5 liter O₂ and held under an atmosphere of oxygen for the full reaction period. CH₃CN (150 μ L) was then added to assist in solubilizing the cobalt complex. After 16 h, the reaction mixture was filtered and the supernatant was concentrated *in vacuo* and then chromatographed (5% EtOAc/petroleum ether) giving 68.6 mg of a red oil which solidified to a orange solid upon standing (69%). The identity of the product, 31, was confirmed by ¹H NMR, mp, HRMS and comparison to authentic sample by HPLC. Purity was established by HPLC at 98%.

EXAMPLE 5

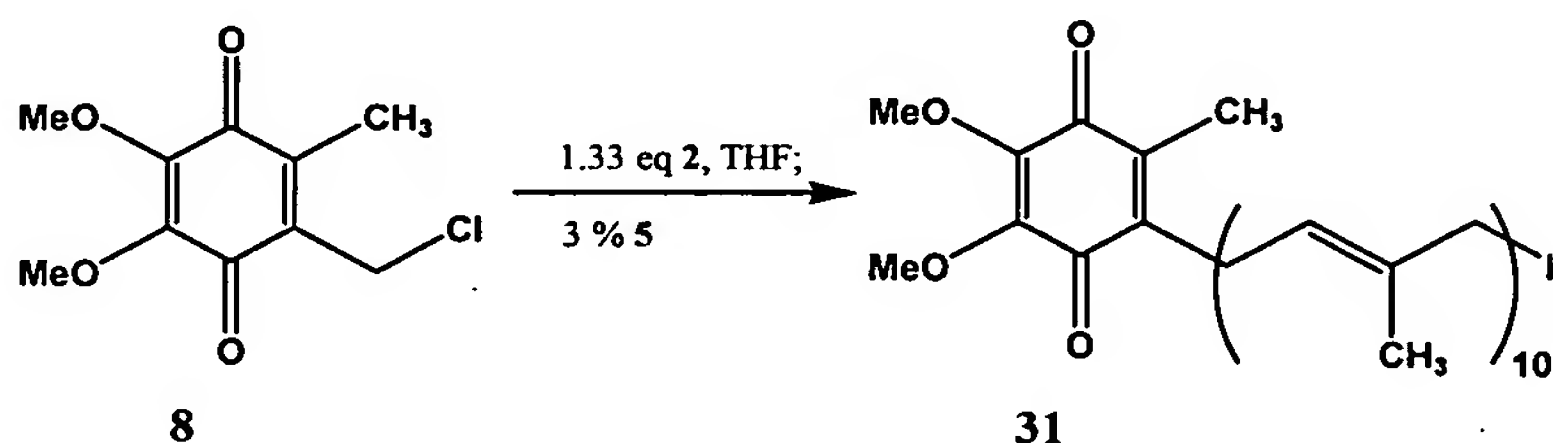
5.1 Carboalumination of alkyne 23



[0143] Cp₂ZrCl₂ (74 mg, 0.25 mmol) and AlMe₃ (0.5 mL, 2.0 M in hexanes, 1.0 mmol) were combined and about 90 % of the solvent was removed *in vacuo*. The gray-white residue was then dissolved in ClCH₂CH₂Cl (DCE) (0.5 mL) giving a pale yellow solution. 23 (325 mg, 0.5 mmol) in DCE (0.25 mL) was added via cannula (exothermic) followed by washings with DCE (2 x 0.125 mL) to complete the transfer. After 11 h at rt, the solvent was completely removed from the heterogeneous yellow mixture *in vacuo*. The residue was triturated with hexanes (3 x 3 mL) and the hexanes removed *in vacuo* to remove all traces of

DCE. To the heterogeneous yellow mixture was then added hexanes (2 mL) and the resulting supernatant was cannulated away from the residual Zr salts. The salts were washed twice with hexanes (2 x 1 mL). The washes were combined with the original wash. The combined clear yellow hexane solution containing the vinylalane **26** was then concentrated *in vacuo* and the residue dissolved in 0.5 mL THF (exothermic) in preparation for the cross-coupling reaction.

5.2 Coupling of Chloromethylated Quinone with Alane



[0144] **8** (86 mg, 0.375 mmol) was dissolved in THF (0.4 mL) and was cannulated into a solution of vinylalane **26**. Two 0.3 mL washings of THF were used to complete the transfer of **8**. The Ni(0) catalyst solution (0.188 mL, 0.011 mmol, 3 mol %) was added at RT *via* syringe. The solution was then protected from light and allowed to stir at RT for more than about 4 h. The reaction was quenched by the addition of EtOAc (10 mL) and 1 M HCl (20 drops). The mixture was stirred for 10 min to break up the aluminum salts (alternatively, a solution containing 0.3 g citric acid/mL water may be used to quench the reaction, followed by extraction with CHCl₃). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organics were combined, washed once with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The resulting yellow oil was subjected to column chromatography (10% EtOAc/petroleum ether) to give 291 mg of **31**, CoQ₁₀, identical in all respects with an authentic sample.

EXAMPLE 6

6.1 Carboalumination of the Alkyne 23

[0145] To a flame dried, argon purged 10 mL RBF was added crude solanesol alkyne, **23** (753 mg of 73% pure material, 0.843 mmol) and Cp₂ZrCl₂ (12 mg, 0.042 mmol) and toluene (0.25 mL) at RT. The RBF was cooled to 5 °C and Me₃Al (2 M in toluene, 1.26 mmol) was added dropwise. Slight smoking was observed and the yellow mixture darkened slightly. The reaction was aged 5 min at 5 °C and then cooled to 0 °C. The homogeneous mixture

was aged 5 min at 0 °C and H₂O (0.75 µL, 0.042 mmol) was added. The reaction smoked slightly and immediately darkened to yellow-orange. The mixture was aged from 0 to 10 °C over 22 h (slow warming from 0 °C) after which TLC (5% DCM/PE) indicated that the alkyne was consumed. A vent needle was inserted to allow evaporation of the toluene under an argon flow, and the reaction was warmed to RT over 30 min during which time it became an orange-yellow paste containing **26**. THF (1.5 mL) was added and the mixture cooled to –15 °C (slightly chunky, yellow-orange) for 10 min.

6.2 Coupling of the Alane **26** and Chloromethyl Quinone **8**

[0146] A pre-cooled (0 °C) solution of **8** (235 mg, 1.01 mmol) in THF (0.5 mL) was added dropwise slowly to a solution containing **26** and 16.5 mg (0.025 mmol) NiCl₂(PPh₃)₂, that had been reduced by 0.050 mmol (2 equiv) n-BuLi. THF (0.5 mL) was used to assist the transfer. The reddish-orange solution was stirred at -15 °C for 3 h during which time the orange color increased. TLC (10% EA: PE) indicated a large CoQ spot, with quinone very faint. The reaction was poured into 0.25 M HCl/Et₂O and stirred 30 min. The aqueous layer extracted with Et₂O (3 x 10 mL) and the combined organics washed with brine, dried (anhydrous MgSO₄), filtered, concentrated *in vacuo*, and purified by flash chromatography (18% Et₂O: PE) to produce **31**, CoQ₁₀ (550 mg, 0.639 mmol, 76% yield, orange solid). Analytical data matched that from previous experiments.

EXAMPLE 7

7.1 Carboalumination of an alkyne **23**

[0147] Crude solanesol alkyne, **23**, was filtered over silica and the solvent (PE) evaporated. The alkyne (4.35 g of 74% pure material, 4.93 mmol, 1 eq) and Cp₂ZrCl₂ (75 mg, 0.26 mmol, 0.05 eq) were added to a flame dried, argon purged 50 mL RBF at RT. The RBF was cooled to 0 °C and Me₃Al (2 M in toluene, 3.75 mL, 7.5 mmol, 1.5 eq) was added dropwise. Slight smoking was observed and after 5-10 min a clear yellow solution was obtained. The homogeneous mixture was stirred for 30 min at 0 °C and H₂O (18 µL, 1 mmol, 0.2 eq) was added. The reaction smoked slightly and immediately darkened to yellow-orange. The mixture was stirred for 20 h at 0 °C, after which time TLC (5% DCM/PE) indicated that the alkyne was consumed. The reaction was warmed to RT and the toluene was evaporated in vacuo over 50 min. The remaining orange-yellow viscous oil containing **26** was solved in THF (10 mL) and the mixture cooled to –20 °C (orange

solution).

7.2 Coupling of the Alane 26 and Chloromethyl Quinone 8

[0148] A pre-cooled (0 °C), pre-generated Ni(0) solution (from NiCl₂ (PPh₃)₂ {98.1 mg, 0.15 mmol, 0.03 eq} and *n*-BuLi {2.5 M in hexane, 0.12 mL, 0.3 mmol, 0.06 eq} in THF {3 mL}) was added dropwise slowly at –20 °C to the previously generated solution of 26, which upon addition turned brown. To this mixture a pre-cooled (0 °C) solution of 8 (1.5 g, 92.1 wt%, 6.01 mmol, 1.2 eq) in THF (3 mL) was added dropwise slowly. The reddish-orange solution was stirred at –15 °C (± 5K) for 2.5 h during which time the orange color increased. TLC (10% EA: PE) indicated a large CoQ₁₀ spot, with quinone very faint. The reaction was poured into 0.25 M HCl/Et₂O (80 mL each) and stirred for 20 min. The aqueous layer was extracted with Et₂O (2 x 80 mL) and the combined organics washed with brine, dried (anhydrous MgSO₄) and filtered. After removal of the solvent in vacuo 5.41 g of crude CoQ₁₀, 31 (59.2 wt%, 75.3 % yield) were obtained as an orange oil.

EXAMPLE 8

8.1 Carboalumination of the Alkyne 23

[0149] Crude solanesol alkyne 23 was filtered over silica and the solvent (PE) evaporated. The alkyne (3.75 g of 76.5% pure material, 4.39 mmol, 1 eq) and Cp₂ZrCl₂ (75 mg, 0.26 mmol, 0.06 eq) were added to a flame dried, argon purged 50 mL RBF at RT. The RBF was cooled to 0 °C and Me₃Al (2 M in toluene, 3.75 mL, 7.5 mmol, 1.7 eq) was added dropwise. Slight smoking was observed and after 5-10 min a clear yellow solution was obtained. The homogeneous mixture was stirred for 30 min at 0 °C and H₂O (13.5 µL, 0.75 mmol, 0.17 eq) was added. The reaction smoked slightly and immediately darkened to yellow-orange. The mixture was stirred for 20 h at 0 °C, after which time TLC (5% DCM/PE) indicated that the alkyne was consumed. The reaction was warmed to RT and the toluene was evaporated *in vacuo* over 50 min. The remaining orange-yellow viscous oil containing 26 was solved in THF (10 mL) and the mixture cooled to –20 °C (orange solution).

8.2 Coupling of the Alane 26 and Chloromethyl Quinone 8

[0150] A pre-cooled (0 °C), pre-generated Ni(0) solution (from NiCl₂ (PPh₃)₂ {98.1 mg, 0.15 mmol, 0.034 eq} and *n*-BuLi {2.5 M in hexane, 0.12 mL, 0.3 mmol, 0.068 eq} in THF {3 mL}) was added dropwise slowly at –20 °C to the previously prepared solution of 26,

which upon addition turned brown. To this mixture a pre-cooled (0 °C) solution of **8** (1.46 g, 95 wt%, 6.01 mmol, 1.36 eq) in THF (3 mL) was added dropwise slowly. The reddish-orange solution was stirred at -15 °C (\pm 5K) for 2.5 h during which time the orange color increased. TLC (10% EA: PE) indicated a large CoQ₁₀ spot, with quinone very faint. The reaction was poured into 0.25 M HCl/Et₂O (80 mL each) and stirred for 20 min. The aqueous layer was extracted with Et₂O (2 x 80 mL) and the combined organics washed with brine, dried (anhydrous MgSO₄) and filtered. After removal of the solvent *in vacuo* 5.05 g of crude CoQ₁₀ **31** (50.5 wt%, 67.2 % yield) were obtained as an orange oil.

EXAMPLE 9

9.1 Carboalumination of the Alkyne 23

[0151] Crude solanesol alkyne **23** was filtered over silica and the solvent (PE) evaporated. The alkyne (4.30 g of 75.9% pure material, 5.0 mmol, 1 eq) was added to a flame dried, argon purged 50 mL RBF at RT and cooled to 0 °C. Me₃Al (2 M in toluene, 3.75 mL, 7.5 mmol, 1.5 eq) was added dropwise and the mixture was shaken. After 10 min a clear yellow solution was obtained, which was allowed to stir for another 25 min at 0 °C. The solution was transferred to a flask containing Cp₂ZrCl₂ (75 mg, 0.26 mmol, 0.05 eq). After stirring for 30 min at 0 °C H₂O (18 μ L, 1 mmol, 0.2 eq) was added. The reaction smoked slightly and immediately darkened to yellow-orange. The mixture was stirred for 20 h at 0 °C, after which time TLC (5% DCM/PE) indicated that the alkyne was consumed. The reaction was warmed to RT and the toluene was evaporated *in vacuo* over 90 min. The remaining orange-yellow viscous oil containing **26** was solved in THF (10 mL) and the mixture cooled to -20 °C (orange solution).

9.2 Coupling of the Alane 26 and Chloromethyl Quinone 8

[0152] A pre-cooled (0 °C), pre-generated Ni(0) solution (from NiCl₂ (PPh₃)₂ {98.1 mg, 0.15 mmol, 0.03 eq} and *n*-BuLi {2.5 M in hexane, 0.12 mL, 0.3 mmol, 0.06 eq} in THF {3 mL}) was added dropwise slowly at -20 °C to the previously prepared solution of **26**, which upon addition turned brown. To this mixture a pre-cooled (0 °C) solution of **8** (1.50 g, 92.1 wt%, 6.01 mmol, 1.2 eq) in THF (3 mL) was added dropwise slowly. The reddish-orange solution was stirred at -15 °C (\pm 5K) for 2.5 h during which time the orange color increased. TLC (10% EA: PE) indicated a large CoQ₁₀ spot, with quinone very faint. The reaction was

poured into 0.25 M HCl/EtOAc (100 mL each) and stirred for 10 min. The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organics washed with brine, dried (anhydrous MgSO₄) and filtered. After removal of the solvent *in vacuo* 5.26 g of crude CoQ₁₀ **31** (57.0 wt%, 69.5% yield) were obtained as an orange oil.

EXAMPLE 10

10.1 Carboalumination of the Alkyne 23

[0153] Crude solanesol alkyne **23** was filtered over silica and the solvent (PE) evaporated. The alkyne (4.25 g of 74.1% pure material, 4.82 mmol, 1 eq) and freshly recrystallized Cp₂ZrCl₂ (75 mg, 0.26 mmol, 0.05 eq) were added to a flame dried, argon purged 50 mL RBF at RT. The RBF was cooled to 0 °C and Me₃Al (2 M in toluene, 5.0 mL, 10 mmol, 2.0 eq) was added dropwise. Slight smoking was observed and after 5-10 min a clear yellow solution was obtained. The homogeneous mixture was stirred for 30 min at 0 °C and H₂O (18 µL, 1 mmol, 0.2 eq) was added. The reaction smoked slightly and immediately darkened to yellow-orange. The mixture was stirred for 20 h at 0 °C, after which time TLC (5% DCM/PE) indicated that the alkyne was consumed. The reaction was warmed to RT and the toluene was evaporated *in vacuo* over 90 min. The remaining orange-yellow viscous oil containing **26** was solved in THF (10 mL) and the mixture cooled to -20 °C (orange solution).

10.2 Coupling of the Alane 26 and Chloromethyl Quinone 8

[0154] A pre-cooled (0 °C), pre-generated Ni(0) solution (from NiCl₂ (PPh₃)₂ {98.1 mg, 0.15 mmol, 0.03 eq} and *n*-BuLi {2.5 M in hexane, 0.12 mL, 0.3 mmol, 0.06 eq} in THF {3 mL}) was added dropwise slowly at -20 °C to the previously generated solution of **26**, which upon addition turned brown. To this mixture a pre-cooled (0 °C) solution of **8** (1.50 g, 92.1 wt%, 6.01 mmol, 1.2 eq) in THF (3 mL) was added dropwise slowly. The reddish-orange solution was stirred at -15 °C (± 5K) for 2.5 h during which time the orange color increased. TLC (10% EA: PE) indicated a large CoQ₁₀ spot, with quinone very faint. The reaction was poured into 0.25 M HCl/EtOAc (100 mL each) and stirred for 20 min. The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organics washed with brine, dried (anhydrous MgSO₄) and filtered. After removal of the solvent *in vacuo* 5.31 g of crude CoQ₁₀ **31** (55.6 wt%, 70.9 % yield) were obtained as an orange oil.

EXAMPLE 11

11.1 Carboalumination of the Alkyne 23

[0155] Crude solanesol alkyne **23** was filtered over silica and the solvent (PE) evaporated. The alkyne (4.25 g of 74.1% pure material, 4.82 mmol, 1 eq) and Cp_2ZrCl_2 (75 mg, 0.26 mmol, 0.05 eq) were added to a flame dried, argon purged 50 mL RBF at RT. The RBF was cooled to 0 °C and Me_3Al (2 M in toluene, 3.0 mL, 6 mmol 1.2 eq) was added dropwise. Slight smoking was observed and after 5-10 min a clear yellow solution was obtained. The homogeneous mixture was stirred for 30 min at 0 °C and H_2O (18 μL , 1 mmol, 0.2 eq) was added. The reaction smoked slightly and immediately darkened to yellow-orange. The mixture was stirred for 20 h at 0 °C, after which time TLC (5% DCM/PE) indicated that the alkyne was consumed. The reaction was warmed to RT and the toluene was evaporated *in vacuo* over 90 min. The remaining orange-yellow viscous oil containing **26** was solved in THF (10 mL) and the mixture cooled to -20 °C (orange solution).

11.2 Coupling of the Alane 26 and Chloromethyl Quinone 8

[0156] A pre-cooled (0 °C), pre-generated Ni(0) solution (from $\text{NiCl}_2(\text{PPh}_3)_2$ {98.1 mg, 0.15 mmol, 0.03 eq} and *n*-BuLi {2.5 M in hexane, 0.12 mL, 0.3 mmol, 0.06 eq} in THF {3 mL}) was added dropwise slowly at -20 °C to the previously generated solution of **26**, which upon addition turned brown. To this mixture a pre-cooled (0 °C) solution of **8** (1.50 g, 92.1 wt%, 6.01 mmol, 1.2 eq) in THF (3 mL) was added dropwise slowly. The reddish-orange solution was stirred at -15 °C ($\pm 5\text{K}$) for 2.5 h during which time the orange color increased. TLC (10% EA: PE) indicated a large CoQ_{10} spot, with quinone very faint. The reaction was poured into 0.25 M HCl/EtOAc (100 mL each) and stirred for 20 min. The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organics washed with brine, dried (anhydrous MgSO_4) and filtered. After removal of the solvent *in vacuo* 5.34 g of crude CoQ_{10} **31** (51.3 wt%, 65.9 % yield) were obtained as an orange oil.

EXAMPLE 12

12.1 Carboalumination of the Alkyne 23

[0157] To a flame dried, argon purged 50 mL RBF was added Me_3Al (2 M in toluene, 3.75 mL, 7.5 mmol 1.5 eq). After cooling to 0 °C water (18 μL , 1 mmol, 0.2 eq) is added

cautiously and stirring was continued for 30 min at 0 °C. The alkyne **23** (4.30 g. of 75.9% pure material, 5.0 mmol, 1 eq) was added to the yellow solution of Me₃Al and water at 0 °C. After stirring for another 30 min (0 °C) the mixture was transferred to a RBF containing Cp₂ZrCl₂ (75 mg, 0.26 mmol, 0.05 eq). The resulting yellow-brown mixture was stirred for 20 h at 0 °C. The reaction was warmed to RT and the toluene was evaporated *in vacuo* over 90 min. The remaining orange-yellow viscous oil containing **26** was solved in THF (10 mL) and the mixture cooled to –20 °C (orange solution).

12.2 Coupling of the Alane 26 and Chloromethyl Quinone 8

[0158] A pre-cooled (0 °C), pre-generated Ni(0) solution (from NiCl₂ (PPh₃)₂ {98.1 mg, 0.15 mmol, 0.03 eq} and *n*-BuLi {2.5 M in hexane, 0.12 mL, 0.3 mmol, 0.06 eq} in THF {3 mL}) was added dropwise slowly at –20 °C to the previously generated solution of **26**, which upon addition turned brown. To this mixture a pre-cooled (0 °C) solution of **8** (1.50 g, 92.1 wt%, 6.01 mmol, 1.2 eq) in THF (3 mL) was added dropwise slowly. The reddish-orange solution was stirred at –15 °C (± 5K) for 2.5 h during which time the orange color increased. TLC (10% EA: PE) indicated a large CoQ₁₀ spot, with quinone very faint. The reaction was poured into 0.25 M HCl/EtOAc (100 mL each) and stirred for 20 min. The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organics washed with brine, dried (anhydrous MgSO₄) and filtered. After removal of the solvent *in vacuo* 5.48 g of crude CoQ₁₀ **31** (45.1 wt%, 57.2 % yield) were obtained as an orange oil.

EXAMPLE 13

13.1 Carboalumination of the Alkyne 23

[0159] Crude solanesol alkyne **23** was filtered over silica and the solvent (PE) evaporated. The alkyne (4.21 g of 77.7% pure material, 5.0 mmol, 1 eq) and freshly recrystallized Cp₂ZrCl₂ (73.1 mg, 0.25 mmol, 0.05 eq) were added to a flame dried, argon purged 50 mL RBF at RT. The RBF was cooled to 0 °C and Me₃Al (2 M in toluene, 3.75 mL, 7.5 mmol 1.5 eq) was added dropwise. Slight smoking was observed and after 5-10 min a clear yellow solution was obtained. The homogeneous mixture was stirred for 30 min at 0 °C and H₂O (13.5 µL, 0.75 mmol, 0.15 eq) was added. The reaction smoked slightly and immediately darkened to yellow-orange. The mixture was stirred for 20 h at 0 °C, after which time TLC (5% DCM/PE) indicated that the alkyne was consumed. The reaction was warmed to RT

and the toluene was evaporated *in vacuo* over 3 h. The remaining orange-yellow viscous oil containing **26** was solved in THF (7 mL) and the mixture cooled to $-20\text{ }^{\circ}\text{C}$ (orange solution).

13.2 Coupling of the Alane **26** and Chloromethyl Quinone **8**

[0160] A pre-cooled ($0\text{ }^{\circ}\text{C}$), pre-generated Ni(0) solution (from $\text{NiCl}_2(\text{PPh}_3)_2$ {98.1 mg, 0.15 mmol, 0.03 eq} and *n*-BuLi {2.5 M in hexane, 0.12 mL, 0.3 mmol, 0.06 eq} in THF {3 mL}) was added dropwise slowly at $-20\text{ }^{\circ}\text{C}$ to the previously prepared solution of **26**, which upon addition turned brown. After aging for 5 min a pre-cooled ($0\text{ }^{\circ}\text{C}$) solution of **8** (1.46 g, 95 wt%, 6.01 mmol, 1.36 eq) containing additional 25% dimethoxychloroquinone (DMCQ) in THF (3 mL) was added dropwise slowly. The reddish-orange solution was stirred at $-15\text{ }^{\circ}\text{C}$ ($\pm 5\text{K}$) for 2 h during which time the orange color increased. TLC (10% EA: PE) indicated a large CoQ₁₀ spot, with quinone very faint. The reaction was poured into 0.25 M HCl/Et₂O (80 mL each) and stirred for 30 min. The aqueous layer was extracted with Et₂O (3 x 80 mL) and the combined organics washed with brine, dried (anhydrous Na₂SO₄) and filtered. After removal of the solvent *in vacuo* 6.07 g of crude CoQ₁₀ **31** (41.3 wt%, 58% yield) were obtained as an orange oil.

EXAMPLE 14

14.1 Carboalumination of the Alkyne **23**

[0161] Crude solanesol alkyne **23** was filtered over silica and the solvent (PE) evaporated. The alkyne (4.00 g of 81.5% pure material, 5.0 mmol, 1 eq) and Cp_2ZrCl_2 (75 mg, 0.26 mmol, 0.05 eq) were added to a flame dried, argon purged 50 mL RBF at RT. The RBF was cooled to $0\text{ }^{\circ}\text{C}$ and Me_3Al (2 M in toluene, 3.75 mL, 7.5 mmol 1.5 eq) was added dropwise. Slight smoking was observed and after 5-10 min a clear yellow solution was obtained. The homogeneous mixture was stirred for 30 min at $0\text{ }^{\circ}\text{C}$ and H₂O (22.5 μL , 1.25 mmol, 0.25 eq) was added. The reaction smoked slightly and immediately darkened to yellow-orange. The mixture was stirred for 20 h at $0\text{ }^{\circ}\text{C}$, after which time TLC (5% DCM/PE) indicated that the alkyne was consumed. The reaction was warmed to RT and the toluene was evaporated *in vacuo* over 90 min. The remaining orange-yellow viscous oil containing **26** was solved in THF (10 mL) and the mixture cooled to $-20\text{ }^{\circ}\text{C}$ (orange solution).

14.2 Coupling of the Alane 26 and Chloromethyl Quinone 8

[0162] A pre-cooled (0 °C), pre-generated Ni(0) solution (from NiCl₂ (PPh₃)₂ {98.1 mg, 0.15 mmol, 0.03 eq} and *n*-BuLi {2.5 M in hexane, 0.12 mL, 0.3 mmol, 0.06 eq} in THF {3 mL}) was added dropwise slowly at –20°C to the previously generated solution of 26, which upon addition turned brown. To this mixture a pre-cooled (0 °C) solution of 8 (1.5 g, 92.1 wt%, 6.01 mmol, 1.2 eq) in THF (3 mL) was added dropwise slowly. The reddish-orange solution was stirred at -15 °C (± 5K) for 2.5 h during which time the orange color increased. The reaction was poured into 0.25 M HCl/EtOAc (100 mL each) and stirred for 10 min. The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organics washed with brine, dried (anhydrous Na₂SO₄) and filtered. After removal of the solvent *in vacuo* 5.25 g of crude CoQ₁₀ 31 (58.2 wt%, 70.8 % yield) were obtained as an orange oil.

[0163] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.